N-(α-AMINOALKYL)BENZOTRIAZOLES: EQUILIBRIA AND REACTIONS

BY

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Dedicated to my parents

Panagyotis and Anna

Αφιερωμενο στους γονεις μου

Παναγιωτη και Αννα

Με αγαπη και σεβασμο

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N-(α-AMINOALKYL)BENZOTRIAZOLES: EQUILIBRIA AND REACTIONS

BY

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Chairman: Alan R. Katritzky
Major Department: Chemistry

Some aspects of the chemistry of benzotriazole have been studied in this work. Several N-(α-aminoalkyl)benzotriazoles have been prepared and studied by IR and NMR spectroscopy in the solid, liquid and gas phases. We have found that the aminoalkyl groups reside at the N-1 position of benzotriazole in the solid state. A rapid isomerization process commences upon changing to the liquid phase, and the aminoalkyl groups interchange between the N-1 and N-2 positions of benzotriazole. By measuring the equilibrium constants in various solvents, we have found that the 1-isomers are generally more stable than the 2-isomers by no more than 1.0 kcal/mole, depending on substituent size and solvent polarity. Small aminoalkyl substituents and polar solvents favor the 1-isomers, whereas 1- and the 2-isomers become sometimes equally favored when compounds with large substituents are dissolved in non-polar solvents.

The isomerization process has been found to occur intermolecularly. On the basis of the spectroscopic evidence,

the proposed mechanism is an ionic process, in which iminium cations and benzotriazole anions are the intermediate species. The required activation energy for the 2- to 1-isomerization has been estimated by coalescence experiments to be in the range between 15.7 to 18.6 kcal/mole, for the examples studied, depending on the electronic features of the substituents and the polarity of the solvents. Stabilization provided to the intermediate iminium ions and benzotriazole anion by electron donating and electron withdrawing substituents, respectively, and by solvation energy in polar solvents, lowers the $\Delta G^{\ddagger}$ values toward the lower limit of the range.

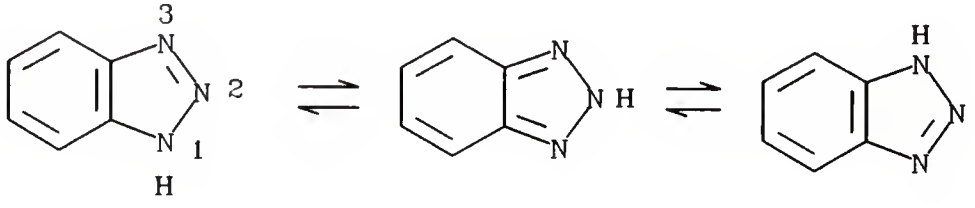
By virtue of their ability to behave as masked iminium ions, N-(α-aminoalkyl)benzotriazoles are reactive toward nucleophiles of various strengths. Thus, reactions with Grignard reagents have produced diversely substituted tertiary amines (aromatic or aliphatic) in high yields. Lithium acetylenides, have replaced benzotriazole to yield otherwise unaccessible 3-alkyl- or 3-aryl-propargyl amines in very good yields. In a similar fashion, Reformatsky reagents afford α- or β-mono or disubstituted β-amino esters in good yields. Finally, several of the benzotriazole adducts have reacted under very mild conditions with secondary amines to produce symmetrical and unsymmetrical aminals, in a reversible process. The produced aminals have been shown to spontaneously disproportionate in polar and non-polar solvents.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Structure and Reactivity of Benzotriazole

Benzotriazole (BtH) is a 1,2,3-triazole fused with a benzene ring across the C-C double bond. The proton attached to the N-atom undergoes annular tautomerism shown by structures (**1.1a**), (**1.1b**), and (**1.1c**). In the parent molecule (and in symmetrically substituted derivatives), position 1 is indistinguishable from position 3, therefore structures (**1.1a**) and (**1.1c**) are identical.



1.1a 1.1b 1.1c

The process is very rapid and the individual tautomers cannot be separated. One tautomeric form, namely (**1.1a**), predominates [84CHC(5)669], [76AHC(S)295]. Specifically, benzotriazole has been found to exist solely in the 1H-tautomeric form in the solid state [74AC1490], and predominantly in the 1H-form in solution [78JCS(P2)312] and in the gas phase [73OMS1267] (K_T = 1H-/2H- >> 1).

Benzotriazole is more acidic (pK_a = 8.2) [51JA4360] than phenol (pK_a = 9.89) [85MI1] and much more acidic than other azoles, for example, benzimidazole (pK_a = 13.2) [58JCS1974], or pyrrole (pK_a = 23) [81JOC632]. The electron withdrawing -N=N- group presumably decreases the electron density on N-1 and renders additional stability to the benzotriazole anion.

Benzotriazole can be alkylated [85H2895] or acylated [84CHC(5)669] easily to give mainly products of 1-substitution. In addition, benzotriazole condenses with formaldehyde and amines to afford Mannich bases. Section 1.3 deals with these compounds in detail.

Aspects of the chemistry of benzotriazole have been studied primarily in two fields:

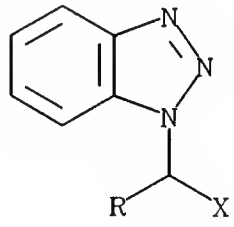
(a) Formation of stable complexes between the parent molecule (or its derivatives) and metals, such as copper, zinc, or silver [81ACS(A)739], [83ICA109]. This property is presumably responsible for the marked anticorrosion activity of benzotriazoles, compounds which are extensively used as corrosion inhibitors and antioxidants. The large number of related patents reflects the interest in this field.

(b) Use of N-hydroxybenzotriazole as an acyl transfer agent in peptide synthesis [77JCS(P2)224]. Due to its enhanced nucleophilicity (α-effect), this molecule readily forms "active" carbamate esters, important synthetic auxiliaries in peptide coupling. On the other hand, benzotriazole derivatives themselves often show marked biological activity (antihypertensives, antidiabetic agents) (see [87JCS(P1)799] and references cited therein).

1.2 Recent Advances in the Chemistry of Benzotriazole

The use of benzotriazole in synthesis has been rather limited. However, considerable progress has been made recently in the chemistry of benzotriazoles, regarding their utilization as synthetic intermediates.

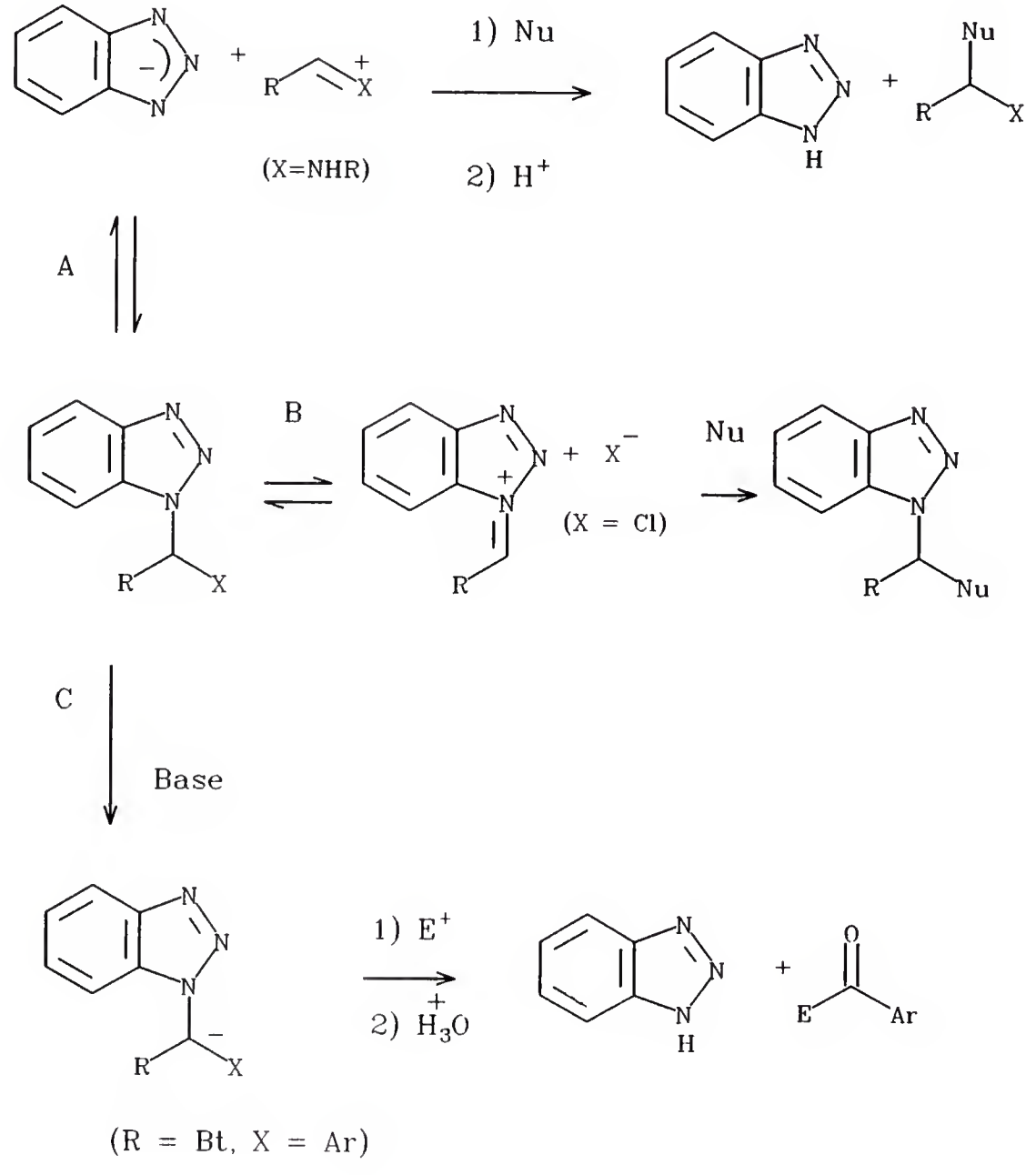
General methods for the preparation of several benzotriazole derivatives, such as α-chloroalkyl-, α-hydroxyalkyl-, α-phenylthioalkyl-, and α-arylaminomethyl-benzotriazoles, and bis(benzotriazolyl)alkanes, have been developed by Katritzky and coworkers [87JCS(P1)781, 799, 805, 811, 819].



X = Cl, OH, SPh, NH-Ar, Bt; R = Alkyl, Aryl

Owing to the both electron-withdrawing (σ_I = 0.55) and electron-donating (σ_R = -0.32 or -0.10) [87AHC1] ability of the Bt-group, a dichotomous behavior of benzotriazole derivatives is expected (Scheme 1.1). In particular, benzotriazole can act as a leaving group, thus providing activation toward Bt-C bond cleavage (path A); alternatively, it could stabilize α-electron deficient

centers (path B); finally, it can also provide moderate stabilization to α-carbanions (path C).



Scheme 1.1

The synthetic potential of benzotriazole derivatives toward reactions with nucleophiles or electrophiles has been successfully exploited in several instances, and applications involving the N-monoalkylation of arylamines [87JCS(P1)805], amides [88JCS(P2)0], thioamides [88TL1755], and the formation of ketones via lithium bis(benzotriazolyl)arenes [87JCS(P1)819] have been published.

1.3 N-(Dialkylaminomethyl)benzotriazoles

The title molecules are easily prepared by the Mannich reaction [73S703], in which benzotriazole (BtH) condenses with formaldehyde and a secondary amine, with concurrent removal of a molecule of water (Equation 1.1) [46JA2496].

$$BtH + CH_2O + HNR_2 \longrightarrow Bt\text{-}CH_2\text{-}NR_2 + H_2O \qquad \text{(Eq. 1.1)}$$

The typical Mannich reaction is carried out in acidic medium, where an iminium ion is considered to be the reactive intermediate (Equation 1.2).

$$CH_2O + HNR_2 \longrightarrow CH_2{=}\overset{+}{N}R_2 \xrightarrow{HNR_2} R_2NCH_2NR_2 \xrightarrow{R'H} R'CH_2NR_2 \qquad \text{(Eq. 1.2)}$$

In basic medium, hydroxymethylamine is postulated as the reactive species (Equation 1.3).

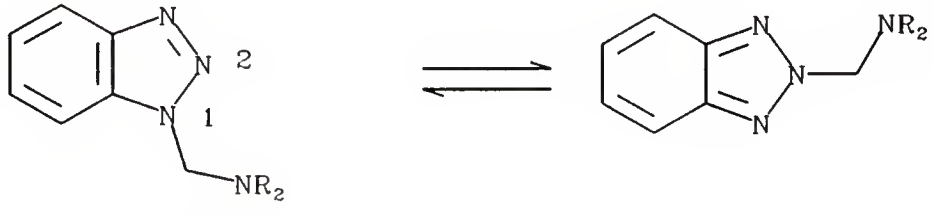
$$CH_2O + HNR_2 \longrightarrow HOCH_2NR_2 \xrightarrow{HNR_2} R_2NCH_2NR_2 \xrightarrow{R'H} R'CH_2NR_2 \qquad \text{(Eq. 1.3)}$$

The reaction does not normally follow the other possible route (Equation 1.4), although some examples are known [73S703].

$$R'H + CH_2O \longrightarrow R'CH_2OH \xrightarrow{HNR_2} R'CH_2NR_2 \qquad \text{(Eq. 1.4)}$$

The Mannich reaction involving benzotriazole does not require addition of acid catalyst [46JA2496]. In cases where dialkylamines are used, the reaction is expected to be base catalyzed (Eq. 1.3). With arylamines, the amino-alkylation is carried out under acidic conditions (added acetic acid or benzotriazole itself serving as the acid catalyst), and evidence exists favoring the intermediacy of a benzotriazolium iminium ion which reacts with the arylamines [87JCS(P1)799].

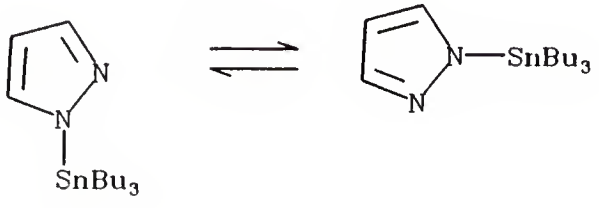
N-[(Benzotriazol-1-yl)methyl]-N,N-dialkylamines (**1.2a**) are of special interest: they spontaneously isomerize to the 2-substituted compounds (1.2b) in solution, and an equilibrium is quickly established (Scheme 1.2). A preliminary investigation of the process has been reported but detailed mechanistic studies have not been carried out [75JCS(P1)1181].



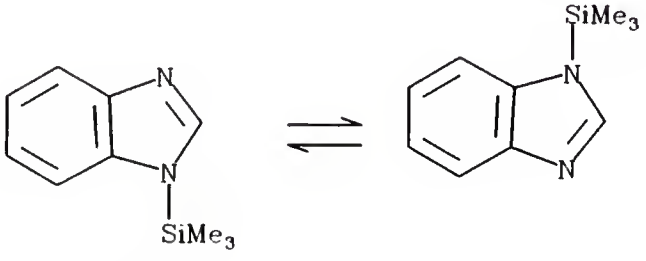
1.2a 1.2b

Scheme 1.2

Analogous examples of azoles undergoing "substituent tautomerism" are few known. In particular, the exchange of the tributylstannyl substituent ("stannotropy") between the two N atoms of pyrazole [compound (1.3), Scheme 1.3] has been described and studied using variable temperature NMR spectroscopy [77JOM69]. The similar isomerization of trialkylsilylbenzimidazole ("silylotropy") [compound (1.4), Scheme 1.3] has been reported [83H1713] as occuring in the solution at room temperature and disappearing in the solid phase. However, a detailed investigation of this process has not been described yet [88MRC134].



1.3



1.4

Scheme 1.3

1.4 Aim of the Work

The main objectives of the research presented in this dissertation were:

(i) To study in detail the isomerization of simple N-[(benzotriazol-1-yl)alkyl]-N,N-dialkylamines of type (**1.2**) in terms of isomeric composition and mechanism of interconversion (Chapter 2).

(ii) To investigate the effect of the structure of several novel N-[α-(benzotriazol-1-yl)alkyl- or -aryl]-N,N-dialkylamines on the isomerization process, as regards both equilibria and kinetics (Chapter 3).

(iii) To develop new synthetic methodologies, using the above benzotriazole adducts as synthetic intermediates in the preparation of tertiary amines, propargylamines, β-amino esters and aminals (Chapters 4, 5, 6 and 7).

CHAPTER 2

THE ISOMERIC COMPOSITION AND MECHANISM OF INTERCONVERSION OF SOME N-(α-AMINOMETHYL)BENZOTRIAZOLE DERIVATIVES

2.1 Introduction

N,N-Disubstituted aminomethylbenzotriazole derivatives (**2.1**) exist in solution as equilibrium mixtures of the corresponding benzotriazol-1-yl- and benzotriazol-2-yl-methylamines (**2.1a**) and (**2.1b**), respectively [75JCS(P1)1181] (Scheme 2.1). While the 1-isomer normally predominates, the position of this equilibrium depends strongly on the polarity of the solvent and also on the substrate structure [75JCS(P1)1181].

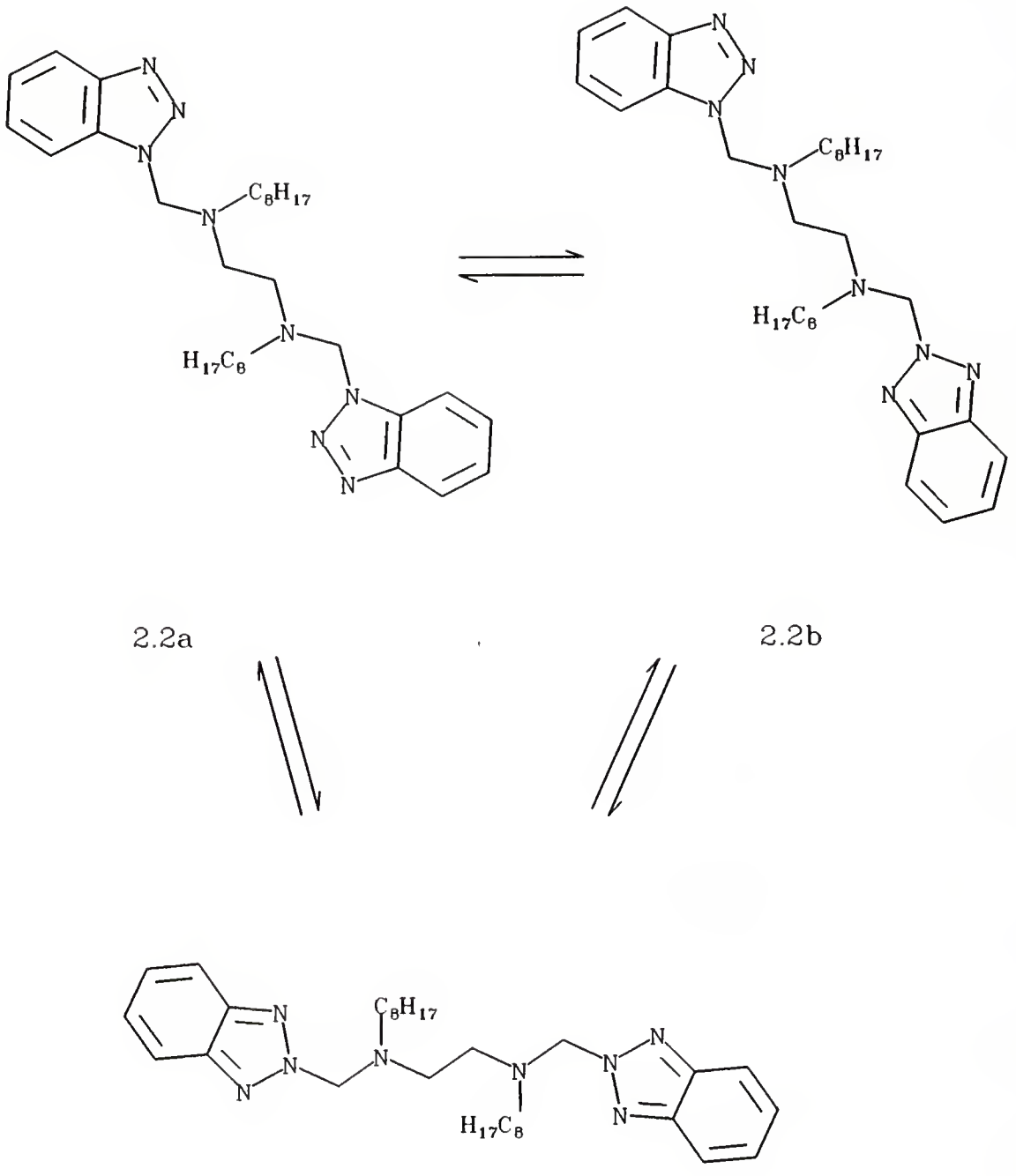
2.1a 2.1b

Scheme 2.1

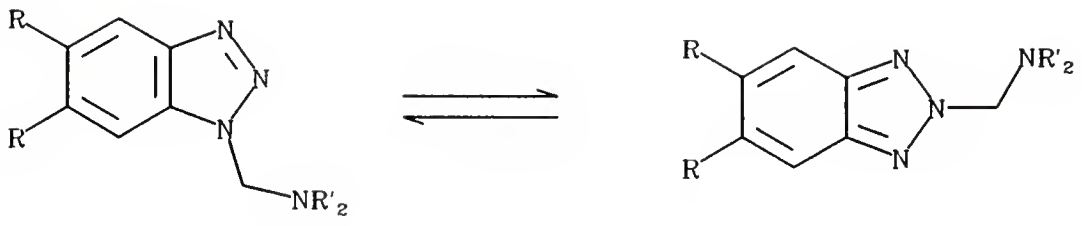
Thus, as the polarity of the medium increases so does the amount of the 1-isomer relative to the 2-isomer, whereas increased bulkiness in the N-aminomethyl substituents favors 2-substitution [75JCS(P1)1181].

Work carried out previously in our group [86UP1] involved the preparation of N,N'-bis(benzotriazolylmethyl)-N,N'-dioctylethylenediamine (2.2) (Scheme 2.2). During the characterization of this compound significant differences in its spectral properties were observed depending on whether (2.2) was in a solid or liquid phase [87JCS(P1)2673]. The data showed that (2.2) existed as a single isomer (2.2a) in the solid state whereas a rapid equilibrium was established upon dissolution to afford a mixture of the isomeric diamines (2.2a), (2.2b) and (2.2c) (Scheme 2.2).

Previous literature [75JCS(P1)1181] on the isomerization of simple N,N-disubstituted aminomethylbenzotriazoles had implied that these compounds existed as single isomers in the solid state and an ionic dissociative mechanism was proposed for their isomerization in solution; however, no evidence for these conclusions was presented. The results obtained with (2.2) [86UP1] prompted us to begin a detailed study on the equilibria of a representative set of N-[(benzotriazol-1-yl)methyl]-N,N-dialkylamines (2.3-2.7) (Scheme 2.3) in the solid, liquid and vapor phases. Our aim was to compare the properties of these compounds in different phases, as well as to elucidate the mechanism of their isomerization.



Scheme 2.2



a b

2.3 R = H, NR'_2 = NMe_2

2.4 R = H, NR'_2 = Pyrrolidyl

2.5 R = Me, NR'_2 = NEt_2

2.6 R = H, NR'_2 = NEt_2

2.7 R = Me, NR'_2 = Pyrrolidyl

Scheme 2.3

2.2 Results and Discussion

2.2.1 Solution Phase

The structure of compounds (2.3-2.7) in solution was studied by IR, ^{1}H- and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectroscopy. The ^{1}H-NMR spectra in deuterochloroform ($CDCl_3$) solutions of (2.3-2.7) exhibited in all cases two singlets of unequal intensity in the region 5.70 to 5.40 ppm, corresponding to the N-CH_2-N protons, and indicating the presence of both the benzotriazol-1-yl and the benzotriazol-2-yl isomers. Compound (2.2) displayed three

such singlets corresponding to the 1,1'- and 2,2'-isomers (**2.2a,c**) and also to the unsymmetrical 1,2'-dioctylethylenediamine (**2.2b**) [87JCS(P1)2673]. The aromatic regions were characteristic of the type of substitution and the resonances were readily assigned to ring protons of the individual isomers. These assignments were based on chemical shifts and coupling constants reported for simple 1- and 2-substituted benzotriazoles [63JCS5556], [80MI1], [69OMR311], [75JCS(P2)1695]. 1-Methylbenzotriazole is a simple Bt-derivative, but its ^{1}H-NMR spectrum is not first order even at 300 MHz. A more appropriate model is 1-hydroxymethylbenzotriazole which displays a typical 1-substitution pattern: H-4 appears as the downfield doublet followed by the doublet of H-7, whereas H-5 and H-6 are the upfield multiplets (Figure 2.1).

On the other hand, 2-methylbenzotriazole shows a characteristic AA'BB' pattern [80MI1] (Figure 2.2), with two multiplets at about 7.5 and 7.3 ppm. Compounds (**2.3-2.7**), as mixtures of the two isomers, show both patterns in the aromatic region. Therefore, doublets at about 8.01 and 7.60 ppm were assigned to H-4 and H-7, respectively, in the ring-unsubstituted-1-substituted isomers, (**2.3a-2.7a**) whereas a multiplet at about 7.90 ppm was due to the same protons in the 2-substituted isomers. A representative ^{1}H-NMR spectrum [of (**2.4**) in $CDCl_3$] is shown in Figure 2.3. The 5,6-dimethylbenzotriazoles (**2.5**) and (**2.7**) showed H-4 and H-7 as two singlets at about 7.80 and 7.35 ppm, respectively, in the 1-isomers, and as one singlet at 7.30 ppm in the 2-isomers.

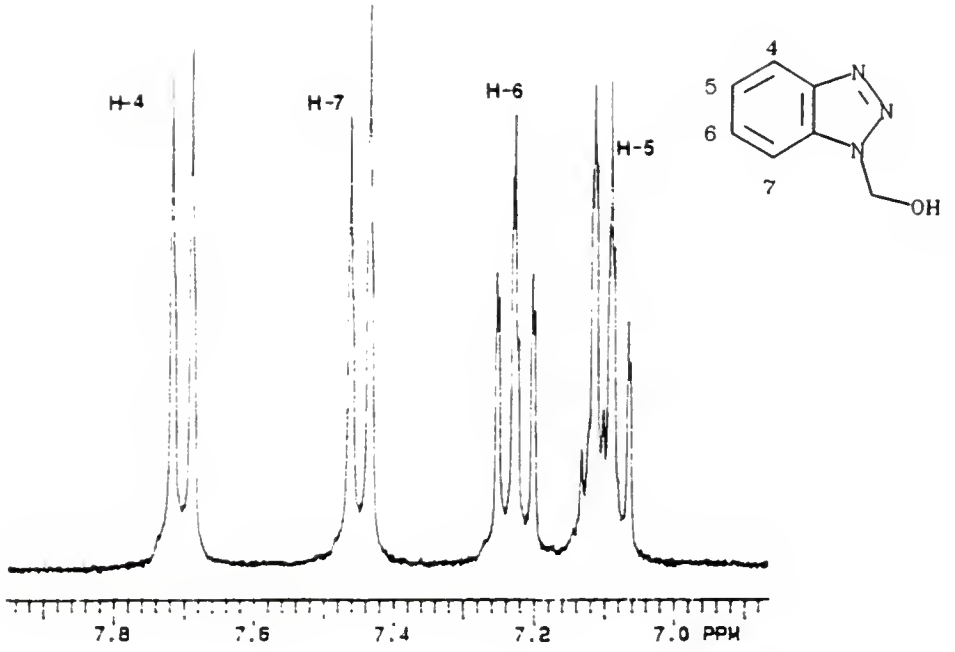


Figure 2.1 Aromatic region of the 300 MHz ^{1}H-NMR spectrum of 1-hydroxymethylbenzotriazole in $CDCl_3$.

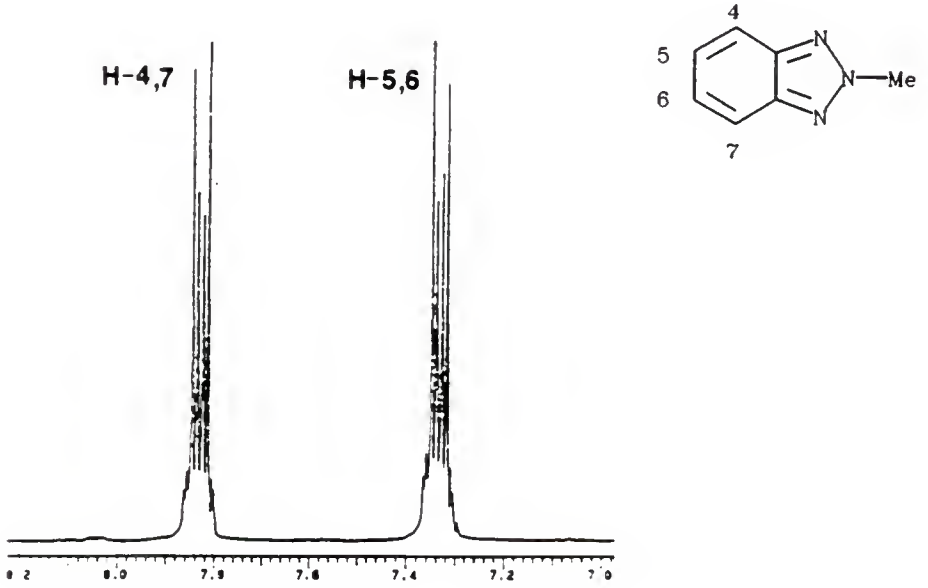


Figure 2.2 Aromatic region of the 300 MHz ^{1}H-NMR spectrum of 2-methylbenzotriazole in $CDCl_3$

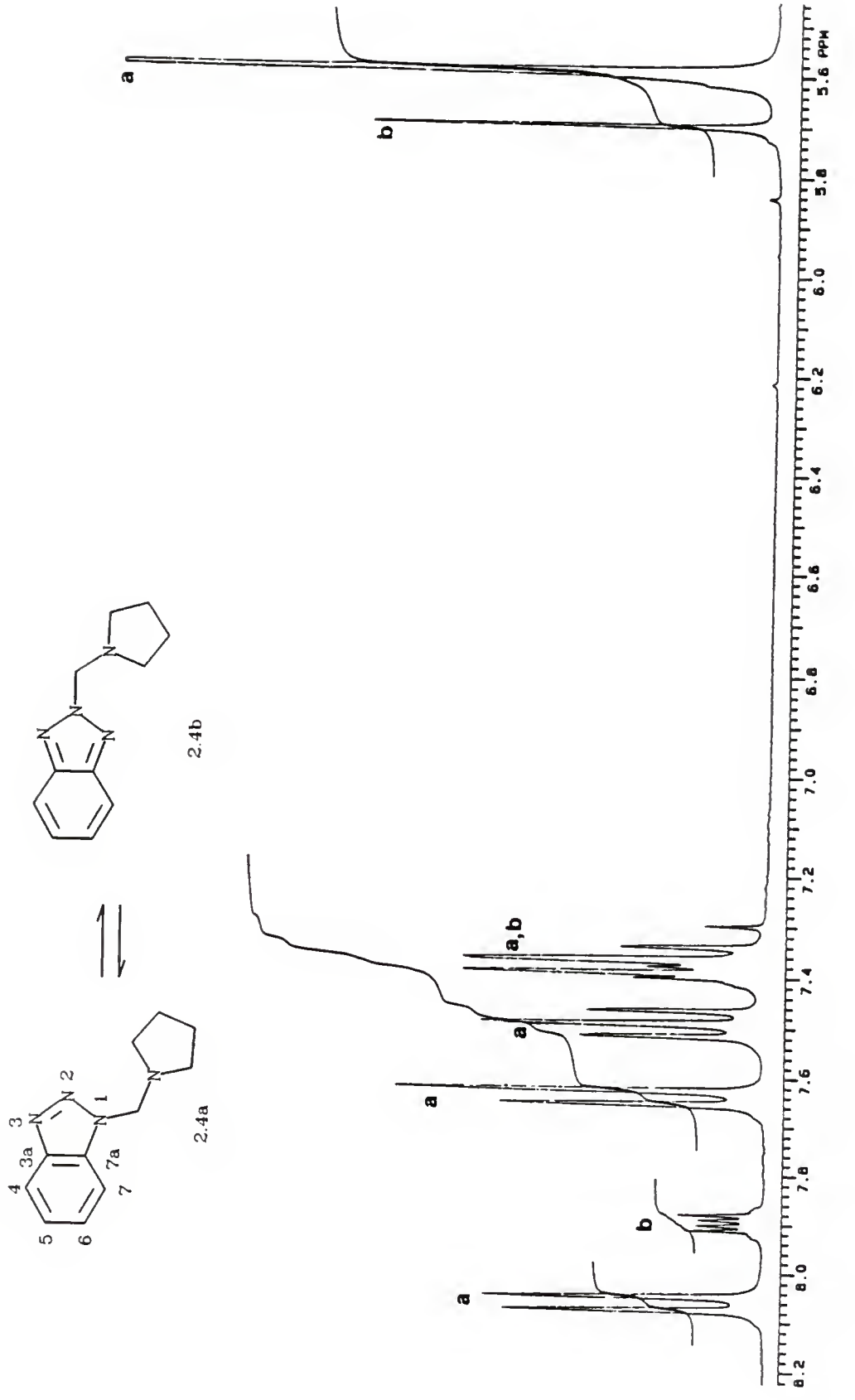


Figure 2.3 Partial 300 MHz ^{1}H-NMR spectrum of N-[(benzotriazol-N-yl)methyl]-pyrrolidine (2.4) in $CDCl_3$.

Also consistent with literature reports [75JCS(P1)1181] is the observation that increasing bulkiness in the N,N-dialkyl substituents (i.e. changing from NMe_2 to pyrrolidino to NEt_2) results in increasing amounts of the 2-substituted isomers. As expected [75JCS(P1)1181], the change from $CDCl_3$ to the more polar solvent dimethyl sulfoxide (DMSO-d_6) resulted in increased amounts of the major 1-substituted isomers at the expense of the 2-substituted ones. Indeed, the concentration of the 2-substituted isomers in DMSO-d_6 was so low that their ^{1}H-NMR signals were frequently obscured: in such cases the ratio of isomers was estimated as >9 favoring the 1-isomer. Table 2.1 shows the ratio [1-isomer]/[2-isomer] as obtained by integration of the signals.

Table 2.1 Isomeric ratios of compounds (2.3-2.7)

Compound	[1-]/[2-] ($CDCl_3$)	[1-]/[2-] (DMSO-d_6)
2.3	4.3	-[a]
2.4	5.5	>9
2.5	2.5	-[a]
2.6	2.2	>9
2.7	5.1	-[a]

[a] The signals of the 2-isomer were totally obscured.

^{13}C-NMR spectroscopy. The aromatic region of the ^{13}C-NMR spectra of 1-substituted benzotriazoles displays an easily recognizable pattern consisting of six signals. Figure 2.4 shows the ^{13}C-NMR spectrum of 1-methylbenzotriazole in $CDCl_3$. When the substituent resides at the 2-position of the ring, as in 2-methylbenzotriazole, the additional symmetry results in only three peaks in that region (Figure 2.5).

The ^{13}C-NMR spectra of compounds (2.2) [87JCS(P1)2673] in $CDCl_3$ displayed nine aromatic signals attributed to a mixture of 1-substituted and 2-substituted benzotriazole groups, while the N$\underline{C}H_2$N region of this molecule contained three signals between 76.0 and 64.0 ppm, one for each of the three isomers. In other solvents the picture of the spectra remained basically the same, the only variations being the intensities of the peaks of the individual isomers, due to solvent dependent changes in the isomeric composition.

Similarly, the ^{13}C-NMR spectra of (2.3-2.7) in both $CDCl_3$ and DMSO-d_6 clearly demonstrated the presence of isomeric mixtures (Figure 2.6). Thus, more than six aromatic carbon signals were observed in all cases and two N-$\underline{C}H_2$-N absorptions appeared in the region 77.5 to 64.7 ppm [see Table 2.2 for ^{13}C-NMR spectra of compounds (2.3-2.7) in $CDCl_3$]. The assignments are concordant with data reported for 1- and 2-substituted bis(benzotriazolyl)methanes [83H1787] and are illustrated in Figures 2.4, 2.5, and 2.6.

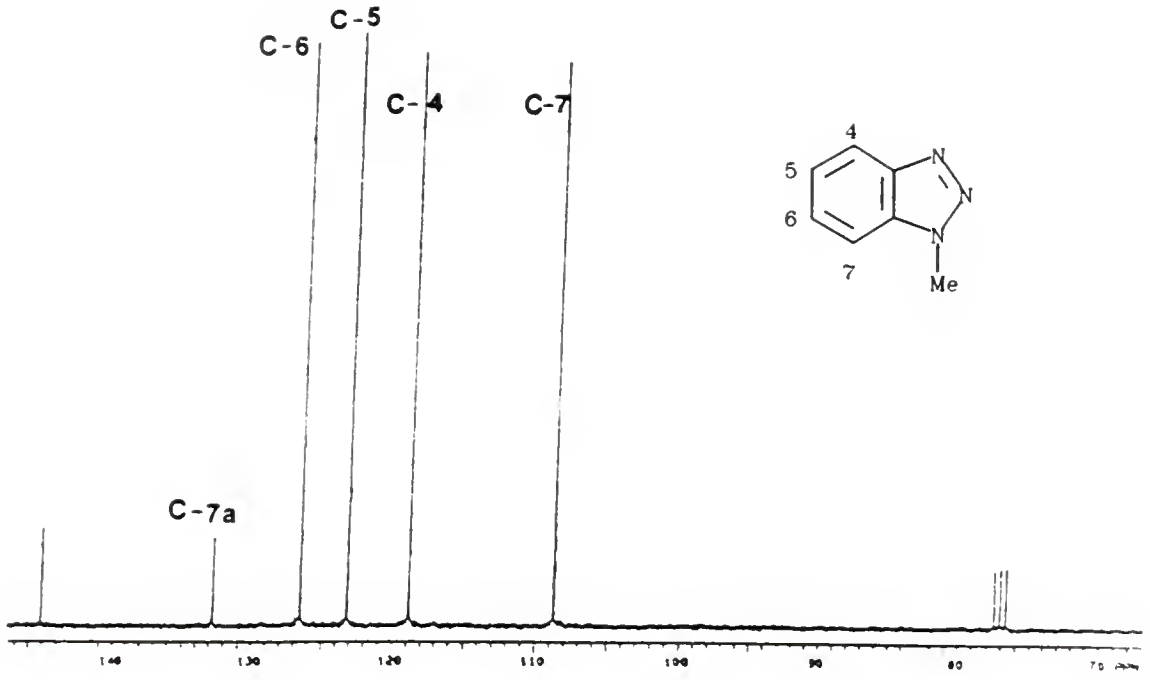


Figure 2.4 Aromatic region of the 75 MHz ^{13}C-NMR spectrum of 1-methylbenzotriazole in $CDCl_3$.

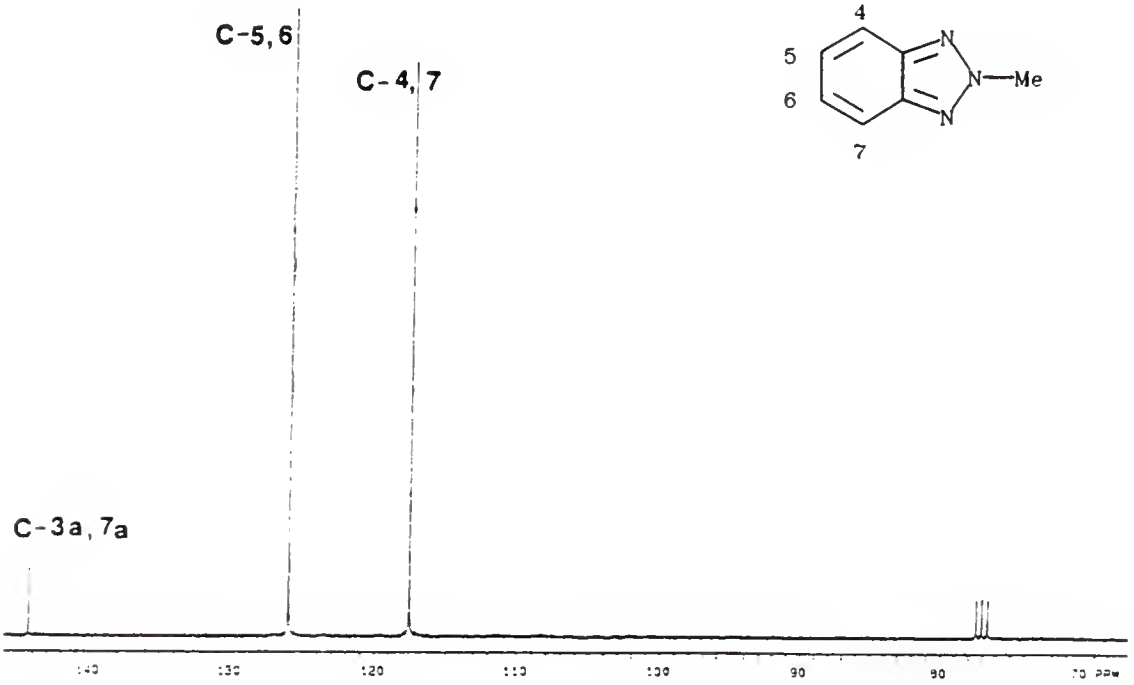


Figure 2.5 Aromatic region of the 75 MHz ^{13}C-NMR spectrum of 2-methylbenzotriazole in $CDCl_3$.

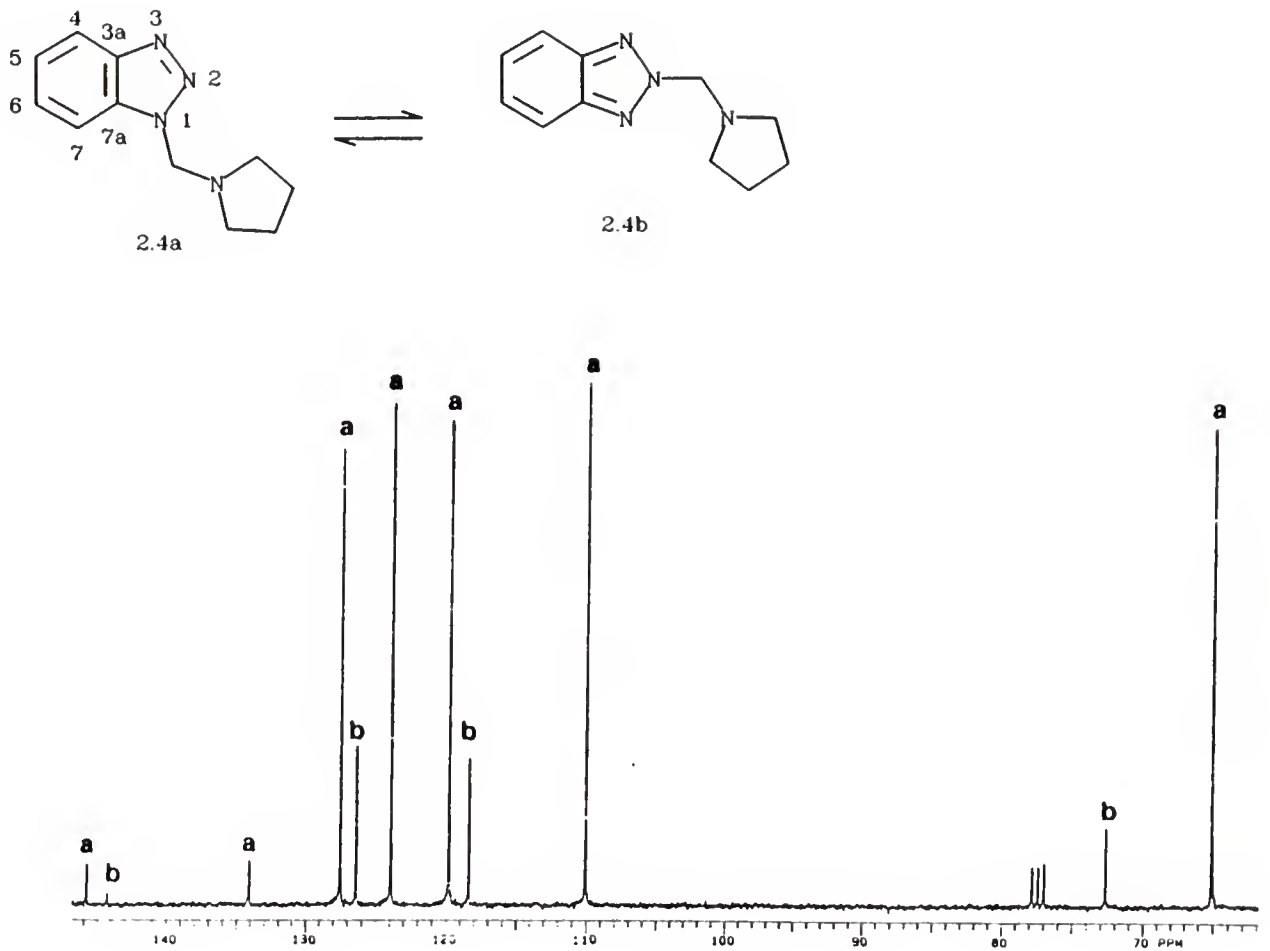


Figure 2.6 Partial 75 MHz ^{13}C-NMR spectrum of N-[(benzotriazol-N-yl)-methyl]pyrrolidine (**2.4**) in $CDCl_3$.

Table 2.2 ^{13}C-NMR spectra of N-[α-(benzotriazol-N-yl)methyl]-N,N-dialkylamines (2.3-2.7).

		1-isomers								
Com.	Solvent	C-3a	C-4	C-5	C-6	C-7	C-7a	NCH_2N	$ArCH_3$	NR'_2
2.3a	$CDCl_3$	145.4	119.4	123.5	127.1	109.7	133.6	69.7	-	42.1
2.3a	DMSO-d_6	144.8	118.9	123.8	127.3	111.1	134.0	69.2	-	41.9
2.4a	$CDCl_3$	145.6	119.6	123.6	127.2	109.8	133.8	65.0	-	50.1, 23.6
2.4a	DMSO-d_6	144.8	118.9	123.8	127.3	110.9	133.9	64.1	-	49.4, 23.2
2.5a	$CDCl_3$	144.9	118.7	137.4	136.4	109.3	133.4	65.1	20.9 20.2	45.4, 12.6
2.5a	DMSO-d_6	144.1	117.8	137.0	136.1	110.0	133.0	64.5	20.3 19.7	44.7, 12.5
2.6a	$CDCl_3$	145.1	119.0	123.1	126.7	109.6	133.2	64.8	-	44.8, 12.1
2.6a	DMSO-d_6	144.9	118.8	123.5	127.0	110.8	133.6	64.7	-	44.7, 12.4
2.7a	$CDCl_3$	144.8	118.6	137.5	136.5	109.1	133.3	64.7	20.6 20.2	50.1, 23.6
2.7a	DMSO-d_6	144.0	117.8	137.2	133.1	110.0	132.9	63.9	20.3 19.8	49.5, 23.2

Table 2.2--Continued.

		2-isomers								
Com.	Solvent	C-3a	C-4	C-5	C-6	C-7	C-7a	NCH_2N	$ArCH_3$	NR'_2
2.3b	$CDCl_3$	143.7	117.9	126.0	126.0	117.9	143.7	77.5	-	41.7
2.3b	DMSO-d_6	-[a]	118.1	126.3	126.3	118.1	-[a]	77.4	-	-[a]
2.4b	$CDCl_3$	144.0	118.1	126.4	126.4	118.1	144.0	72.5	-	49.3, 23.9
2.4b	DMSO-d_6	-[a]	117.8	126.1	126.1	117.8	-[a]	71.9	-	48.6, -[b]
2.5b	$CDCl_3$	143.4	116.6	132.8	132.8	116.6	143.4	71.6	20.7	45.7, 12.8
2.5b	DMSO-d_6	142.8	116.3	132.7	132.7	116.3	142.8	71.0	20.2	45.2, 12.8
2.6b	$CDCl_3$	143.5	117.7	125.5	125.5	117.7	143.5	71.4	-	45.2, 12.4
2.6b	DMSO-d_6	-[a]	117.9	126.0	126.0	117.9	-[b]	71.4	-	45.2, -[b]
2.7b	$CDCl_3$	143.4	116.5	136.5	136.5	116.5	143.4	72.1	20.6 20.2	49.4, 23.8
2.7b	DMSO-d_6	-[b]	116.4	-[b]	-[b]	116.4	-[b]	71.6	20.3 19.8	48.7, 23.6

[a] Too weak to be detected. [b] Obscured by signals of the 1-isomer.

Infrared spectroscopy. IR has been used previously to distinguish between 1- and 2-substituted benzotriazole derivatives [63HCA1473], [87JCS(P1)811]. The 1-isomers typically display two weak absorptions in the region 1630 to 1550 cm^{-1} (where the C=C and C=N stretching vibrations are most probably located), whereas the 2-isomers show instead one weak absorption in the same region. The infrared spectra of bromoform or chloroform solutions of (2.3-2.7) (Figure 2.7) displayed in all cases all three of these absorption bands supporting the presence of both the benzotriazol-1-yl and the benzotriazol-2-yl isomers in solution. A similar behavior was demonstrated by 1,1'-, 1,2'- and/or 2,2'-bis(benzotriazolylmethyl) derivatives (2.2) [87JCSP(1)2673].

Compound (2.6) is a liquid at 25 °C: the infrared spectrum of a neat film shows in the region 1630 to 1550 cm^{-1} three absorptions at 1625, 1588 and 1569 cm^{-1}, indicating that in the liquid state, just as in solution, N-[(benzotriazolyl)methyl]-N,N-dialkylamines exist as mixtures of two isomers.

The weak C=N, C=C and N=N absorptions of compounds (2.3), and (2.6) could be clearly detected only by an FT instrument, while signals of (2.2) were detectable by a conventional spectrometer. Data are collected in Table 2.3.

Table 2.3. IR data of N-[(benzotriazolyl-N-yl)methyl]-N,N-dialkylamines (2.2), (2.3), (2.6) and (2.7).

Comp.	$CHCl_3$ solution	Neat or melt	Ar matrix	KBr
2.2[a]	1610 1590 1565	1610 1590 1565	-	1610 1590
2.3[b]	1618 1592 1519	-	1616 1590 1517	1615 1587
2.6[b]	1625 1590 1570	1625 1588 1569	-	-
2.7[b]	1627 1582 1552	-	-	1631 1585

[a] Bromoform solution. [b] FT spectra.

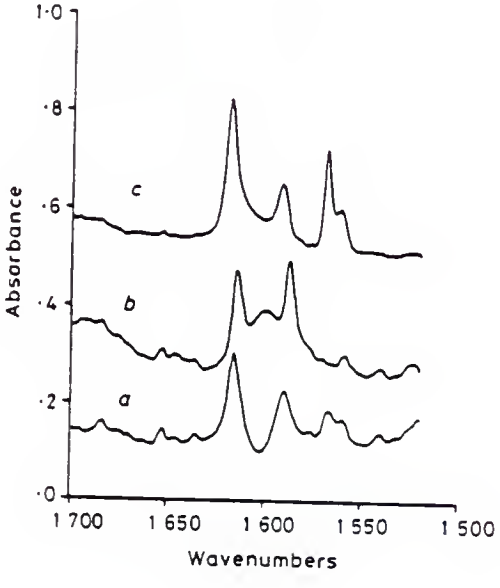


Figure 2.7 FT-IR spectrum of N-[(benzotriazol-N-yl)-methyl]-N,N-dimethylamine (2.3): (a) 0.3 M solution in $CHCl_3$; (b) KBr pellet; (c) Ar matrix spectrum.

2.2.2 Solid Phase

Infrared spectroscopy. The infrared spectra of the aminomethylbenzotriazoles (2.3-2.7) in KBr discs (Table 2.3, Figure 2.7) each displayed only two absorptions at 1570 to 1550 cm^{-1} in agreement with their benzotriazol-1-yl- structures. Similarly, examination of (2.2) in a KBr disc, or in a nujol dispersion, showed the presence of only two weak absorptions at 1610 and 1590 cm^{-1} in the diagnostic region 1630-1550 cm^{-1}, as expected for a 1,1'-bisbenzotriazolyl derivative [63HCA1473], [87JCS(P1)1811]. In particular, no absorption was found in the region 1570 to 1550 cm^{-1} confirming the absence of benzotriazol-2-yl groups. The IR results agree with the structure of N,N'-[1,1'-bis(benzotriazolylmethyl)]-N,N'-dioctylethylenediamine (2.2a) determined by an X-ray analysis [87JCS(P1)2673].

^{13}C-NMR spectroscopy. The solid state ^{13}C-NMR spectra of compounds (2.3), (2.4) and (2.5) were also examined. The spectrum of compound (2.5) showed a simple 1:1 correspondence between the six signals and the aromatic carbon atoms. The spectra of compounds (2.3) and (2.4) showed asymmetric splitting in the peaks attributable to atoms C-3a and C-methyl [compound (2.3)], and C-5 or C-6 [compound (2.4)]. The lack of correlation of carbon types for which splittings were observed suggests that these

features are due to crystallographic factors and do not indicate the presence of two isomers. Thus, the solid state NMR results also support the existence of only the 1-isomer in the solid phase.

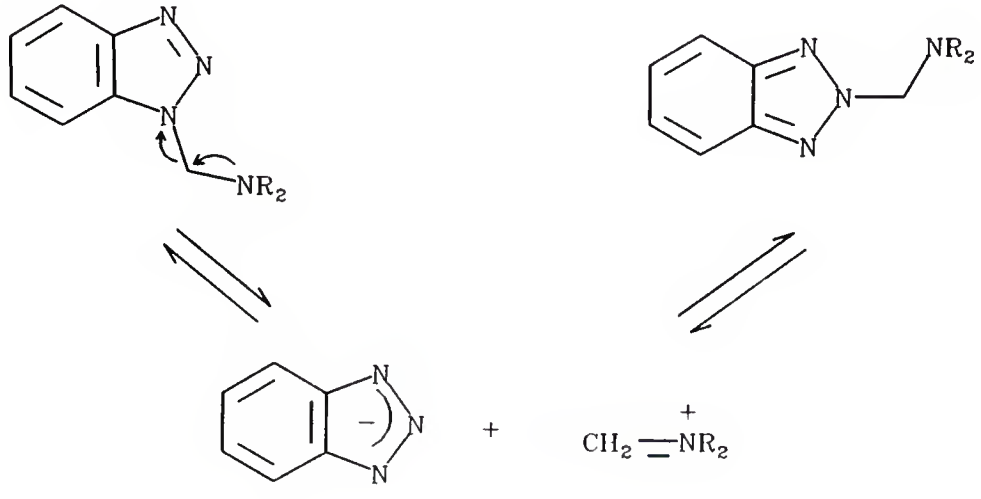
2.2.3 Inert Gas Matrix Phase

Infrared spectroscopy of (2.3) condensed in an inert gas matrix (where molecular interactions are negligible) was used as an approximation for the study of the properties of this compound in the gas phase. Thus, the infrared spectrum of (2.3) in an Ar matrix showed the presence of the characteristic three bands diagnostic of both the 1- and 2-benzotriazole isomers (Figure 2.7).

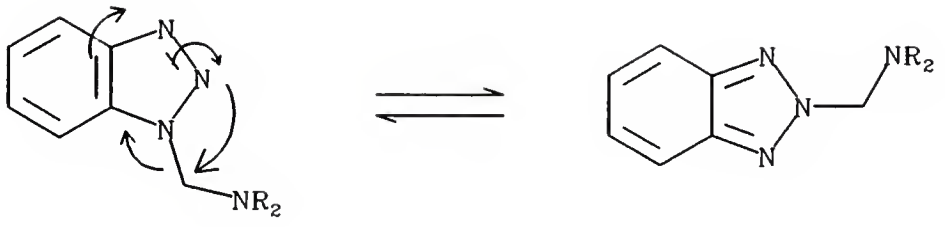
2.2.4 Mechanistic Studies

The most likely mechanism for the isomerization observed in the liquid and solution phases is a dissociation-recombination process (Scheme 2.4) [75JCS(P1)1181] but a concerted mechanism (Scheme 2.5) had not been previously ruled out. To distinguish between these two possibilities, a cross-over experiment was carried out by mixing together $CDCl_3$ or DMSO-d_6 solutions of (2.4) and (2.5) and examining the mixtures by ^{1}H- (Table 2.4) and ^{13}C- (Table 2.5) NMR spectroscopy. These spectra revealed the presence of eight compounds that could be readily assigned as both the 1- and 2-isomers of each of (2.4), (2.5), (2.6) and (2.7), by

direct comparison with the spectra of the individual pairs. The relative intensities (Tables 2.4 and 2.5) are also consistent with these assignments. As expected, the 1-isomers predominate in $CDCl_3$ and even more so in the more polar DMSO-d_6. The ^{1}H-NMR spectrum ($CDCl_3$) of the mixture (Table 2.4) showed only seven of the expected eight peaks in the N-CH_2-N region 5.70 to 5.30 ppm. The missing signal is apparently hidden under the rather broad peak at 5.60 ppm. In DMSO-d_6 the N-CH_2-N signals for the 2-isomers are obscured by the corresponding 1-isomer signals (see above), and only four signals corresponding to the 1-isomers are observed.



Scheme 2.4



Scheme 2.5

Table 2.4 ^{1}H-NMR data for the N-CH_2-N group of compounds (2.4-2.7) from the cross-over experiment.

Assignment	2-isomers			1-isomers			
	2.4	2.6,2.7	2.5	2.4	2.7	2.6	2.5
δ ($CDCl_3$)	5.7	5.6	5.5	5.5	5.5	5.5	5.4
Area (%)	4	9	6	23	23	18	17
δ (DMSO-d_6)	-	-	-	5.7	5.6	5.6	5.4
Area (%)	-	-	-	37	25	24	15

The ^{13}C-NMR spectrum (Table 2.5) provided more widely separated peaks. The N-CH_2-N carbons appeared in $CDCl_3$ as two groups of four signals each between 71.7 and 70.5 ppm, and 64.6 to 63.8 ppm, corresponding to the 2- and 1-isomers, respectively. The ratios were measured by integration of these signals in a quantitative experiment. Figure 2.8 shows the region of the NCH_2N after mixing (2.4) and (2.5)

in deuterated chloroform. In DMSO-d_6 the signals for the 2-isomers were too weak to allow precise measurements. An identical equilibrium mixture as regards both chemical shifts and ratios was obtained by mixing together solutions of (2.6) and (2.7).

Table 2.5 ^{13}C-NMR data for the N-CH_2-N groups of benzotriazoles (2.4-2.7) from the cross-over experiment.

Assignment	2-isomers				1- isomers			
	2.4	2.7	2.5	2.6	2.5	2.6	2.4	2.7
δ($CDCl_3$)	71.7	71.2	71.0	70.6	64.4	64.2	64.1	63.9
Area(%)	4	4	5	5	18	17	24	22
δ (DMSO)	-	-	-	-	64.5	64.8	64.1	64.0
Area (%)	-	-	-	-	25	29	25	21

Temperature Effect. The ^{1}H-NMR spectra of (2.5), (2.6) and (2.7) were also recorded at -50 °C and at 40 °C in $CDCl_3$ and the ratios of isomers measured. The results indicate no significant change in the isomer distribution or in the shape of the signals with respect to the data obtained at 25°C. Modification in the structure of the compounds resulted in marked temperature effects, as shown in Chapter 3.

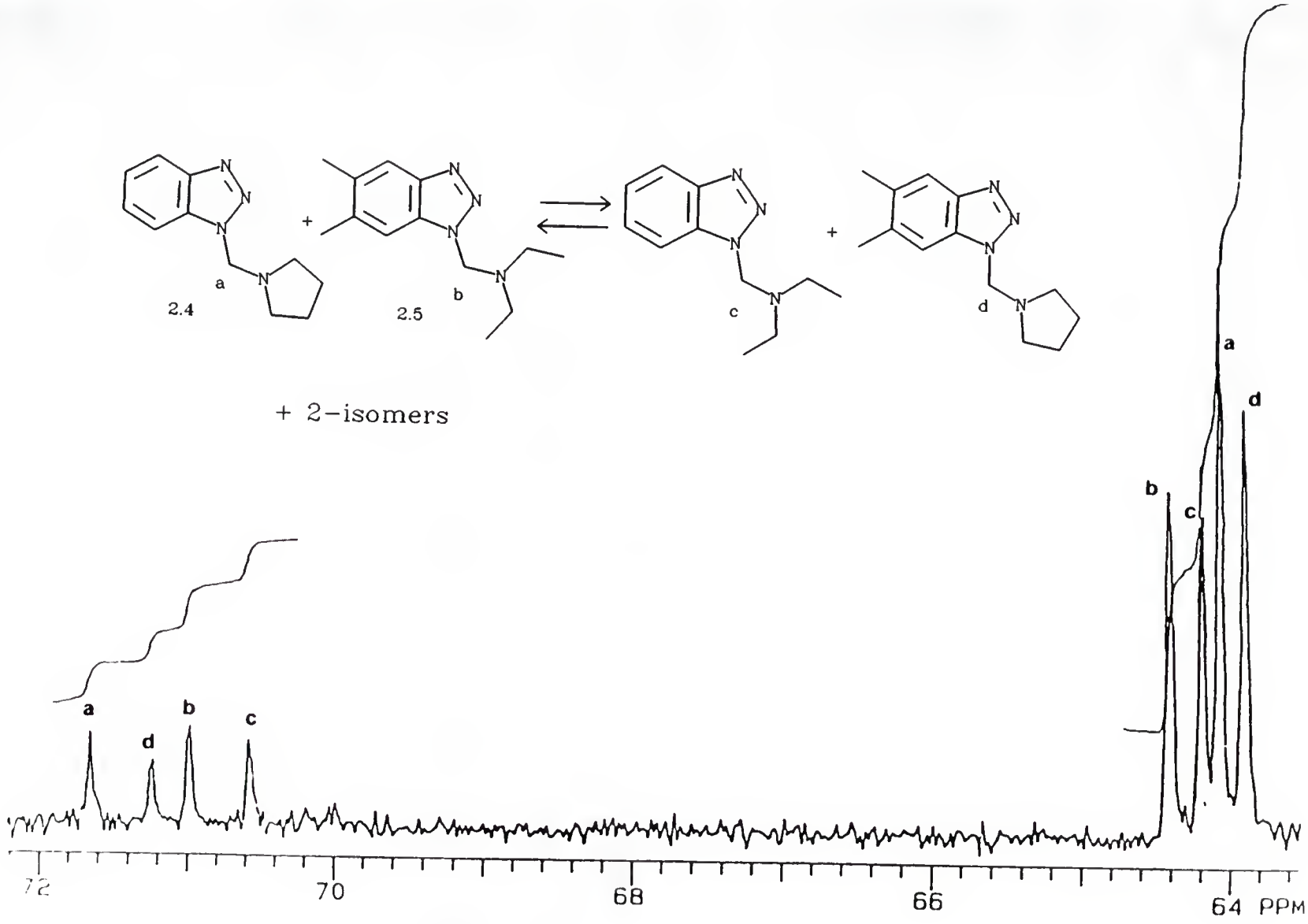


Figure 2.8 50 MHz ^{13}C-NMR spectrum ($N\underline{C}H_2N$ region) of the mixture of (2.4) and (2.5) in $CDCl_3$.

2.3 Conclusions

The work described in this chapter shows that N-[(benzotriazol-N-ylmethyl]-N,N-dialkylamines exist as single benzotriazol-1-yl- isomers in the solid phase. However, in liquid, solution and vapor phases these compounds undergo isomerization and mixtures of the benzotriazol-1-yl- and benzotriazol-2-yl- isomers are observed. Our studies prove that the isomerization process is intermolecular and are consistent with a dissociative pathway to iminium ions and the benzotriazole anion. The subsequent recombination of these two species furnishes equilibrium mixtures of benzotriazol-1-yl- and benzotriazol-2-yl- isomers in which the 1-isomers always predominate.

2.4 Experimental

2.4.1 Instruments and Methods

Melting points were determined on a Kofler hot-stage microscope, and are uncorrected. IR spectra were recorded on a FT-IR Nicolet 7000 Series spectrometer; measurements were done with 0.3 M $CHCl_3$ or $CHBr_3$ solutions, or 1% KBr pellet; the argon matrix experiment was recorded at 24°K and 10^{-7} mm Hg was carried out by Dr. M. Szczesniak of this department [87JCS(P1)2376], who also operated the FT-IR instrument.

^{1}H- (200 MHz) and ^{13}C- (50 MHz) solution NMR spectra were recorded on a Varian XL 200 spectrometer. Cross-over experiments were carried out by mixing equimolar solutions of both substrates. Quantitative ^{13}C-NMR spectra were acquired at 50 MHz using a 5 sec pulse delay. Low temperature ^{1}H-NMR spectra were obtained at 100 MHz using a Jeol FX-100 spectrometer under the guidance of Dr. King of this department.

Solid state ^{13}C-NMR spectra were acquired on a modified Varian XL 200 NMR spectrometer using cross polarization and magic angle spinning (CPMAS) [87JCS(P1)2673] by Dr. R. Skarjune at 3M company.

Spectra displayed in Figures 2.1-2.6 were recorded on a Varian VXR 300 NMR instrument for better presentation.

2.4.2 Preparation of N-[(Benzotriazol-N-yl)methyl]-N,N-dialkylamines

General method. All compounds were prepared according to a general literature procedure [46JA2496] by stirring equimolar amounts of a secondary amine, 37% aq. formaldehyde and benzotriazole in methanol for 24 h. Evaporation of the solvent under reduced pressure gave the product. ^{13}C-NMR and IR data are given in Tables 2.2 and 2.3, respectively.

N-[(Benzotriazol-N-yl)methyl]-N,N-dimethylamine (2.3). The product was obtained as a white crystalline solid (97%), m.p. 95-98°C (from diethyl ether) (lit. [75JCS(P1)1181] m.p. 98-100°C); δ_H ($CDCl_3$) 1-isomer, 8.07 (d, J = 8 Hz,

H-4), 7.62 (d, J = 8 Hz, H-7), 7.49 (m, H-5), 7.41 (m, H-6, overlapping with signals of the 2-isomer), 5.40 (s, NCH_2N), 2.40 (s, CH_3); 2-isomer, 7.90 (AA' m, H-4, H-7), 7.49 (m, H-5,6, obscured by signals of 1-isomer), 5.51 (s, NCH_2N), 2.46 (s, CH_3).

N-[(Benzotriazol-N-yl)methyl]pyrrolidine (2.4). The product was collected as a white solid (98%), m.p. 79-81°C (from diethyl ether) (Found, C, 65.66; H, 7.29; N, 27.88%. $C_{11}H_{14}N_4$ requires, C, 65.32; H, 6.98; N, 27.70%); δ_H ($CDCl_3$) 1-isomer, 8.01 (d, J = 8 Hz, H-4), 7.60 (d, J = 8 Hz, H-7), 7.44 (t, J = 7 Hz, H-5), 7.30 (t, J = 7 Hz, H-6), 5.51 (s, NCH_2N), 2.75 [m, $N(C\underline{H}_2CH_2)_2$], 1.72 [m, $(NCH_2C\underline{H}_2)_2$)]; 2-isomer, 7.87 (m, H-4, H-7), 7.38 (m, H-5,6, obscured by signals of 1-isomer), 5.70 (s, NCH_2N), 2.87 [m, $N(C\underline{H}_2CH_2)_2$], 1.72 [m, $N(CH_2C\underline{H}_2)_2$].

N-[(5,6-Dimethylbenzotriazol-N-yl)methyl]-N,N-diethylamine 2.5). It was obtained as a pale yellow powder (91%), m.p. 95-98°C (from diethyl ether) (Found, C, 67.99; H, 8.44; N, 24.47%. $C_{13}H_{18}N_4$ requires, C, 67.80; H, 7.88; 24.33%); δ_H ($CDCl_3$) 1-isomer, 7.77 (s, H-4), 7.35 (s, H-7), 5.44 (s, NCH_2N), 2.66 [q, J = 7 Hz, $N(C\underline{H}_2CH_3)_2$], 2.42 (s, ring $-CH_3$), 2.39 (s, ring $-CH_3$), 1.14 [t, J = 7 Hz, $N(CH_2C\underline{H}_3)_2$]; 2-isomer, 7.62 (s, H-4, H-7), 5.57 (s, NCH_2N), 2.68 [q, J = 7 Hz, $N(C\underline{H}_2CH_3)_2$], 2.39 (s, ring $-CH_3$), 1.16 [t, J = 7 Hz, $N(CH_2C\underline{H}_3)_2$].

N-[(Benzotriazol-N-yl)methyl]-N,N-diethylamine (2.6). The oily product was dried under vacuum over P_2O_5 (96%), b.p. 120-124°C (at 0.65 mm Hg) (Found, C, 64.17; H, 7.73; N, 27.79%. $C_{11}H_{16}N_4$ requires, C, 64.68; H, 7.89; N, 27.43%); δ_H ($CDCl_3$) 1-isomer, 8.05 (d, J = 8 Hz, H-4), 7.62 (d, J = 8 Hz, H-7), 7.48 (t, J = 8 Hz, H-5), 7.36 (t, J = 8 Hz, H-6), 5.52 (s, NCH_2N), 2.68 [q, J = 7 Hz, $N(C\underline{H}_2CH_3)_2$], 1.15 [t, J = 7 Hz, $N(CH_2C\underline{H}_3)_2$]; 2-isomer, 7.91 (m, H-4, H-7), 7.36 (m, H-5,6, obscured by signals of 1-isomer), 5.64 (s, NCH_2N), 2.68 [q, J = 7 Hz, $N(C\underline{H}_2CH_3)_2$], 1.15 [t, J = 7 Hz, $N(CH_2C\underline{H}_3)_2$].

N-[(5,6-Dimethylbenzotriazol-N-yl)methyl]pyrrolidine (2.7). A beige solid was obtained (88%), m.p. 39-41°C (from petroleum ether, b.p. 40-60°C) (Found, C, 67.01; H, 8.98; N, 24.13%. $C_{13}H_{20}N_4$ requires, C, 67.21; H, 8.68; N, 24.11%); δ_H ($CDCl_3$) 1-isomer, 7.79 (s, H-4), 7.37 (s, H-7), 5.51 (s, NCH_2N), 2.75 [m, $N(C\underline{H}_2CH_2)_2$], 2.43 (s, ring CH_3), 2.40 (s, ring $-CH_3$), 1.72 [m, $N(CH_2C\underline{H}_2)_2$]; 2-isomer, 7.62 (s, H-4, H-7), 5.63 (s, NCH_2N), 2.84 (s, ring $-CH_3$), 2.84 [m, $N(C\underline{H}_2CH_2)_2$], 1.72 [m, $N(CH_2C\underline{H}_2)_2$].

CHAPTER 3

INFLUENCE OF STRUCTURE ON THE ISOMERIZATION OF N-[α-(BENZOTRIAZOL-N-YL)ALKYL]-N,N-DIALKYLAMINES

3.1 Introduction

The isomerization of N-(benzotriazol-N-ylmethyl)-N,N-dialkylamines was investigated and discussed in Chapter 2. The responsible dissociative process was convincingly explained by the intermediacy of iminium ions and the benzotriazole anion (Scheme 2.4, Chapter 2).

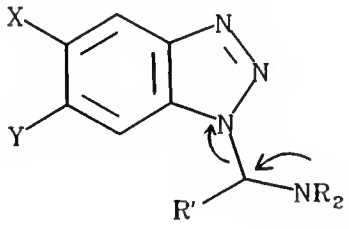
As an extension of that work, the present chapter reports a study of the ^{1}H-NMR spectra of a series of benzotriazole adducts at variable temperatures, it provides estimates of the $\Delta G^{\ddagger}$ values for the isomerization process, and discusses the parameters affecting the rates and equilibrium positions of the dissociation process as a function of the molecular structure. In particular, we examine series of compounds with the objective of evaluating the effects of the following features:

(a) The influence of the solvent on the magnitude of $\Delta G°$ and $\Delta G^{\ddagger}$.

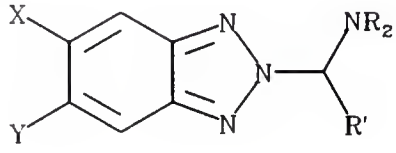
(b) The effect of the electron-withdrawing or -donating character of α-substituents (R') in the iminium ion intermediate, or in the benzotriazole benzene ring (X, Y) on $\Delta G^{\ddagger}$ [see generalized structures (3.1), Scheme 3.1].

(c) The change in $\Delta G°$ as a function of the size of R and R′.

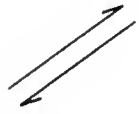
(d) The correlation between $\Delta G^{\ddagger}$ and the basicity of the corresponding amine HNR_2.

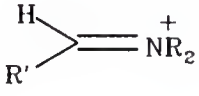


3.1a



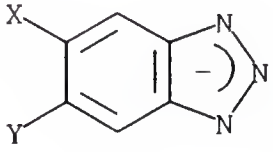
3.1b





3.2

+



3.3

Scheme 3.1

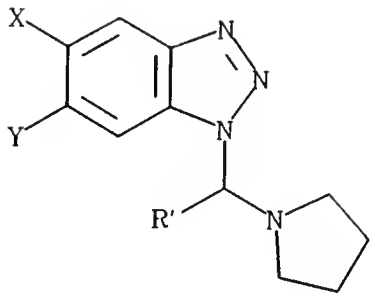
In the case of adducts (3.1) the energy barrier of the equilibrium (3.1a) to (3.1b) (Scheme 3.1) should be lower than in the case of the (2.1a) to (2.1b) interconversion

(Scheme 2.1, Chapter 2): the R' group stabilizes the intermediate iminium ion (3.2) compared to the unsubstituted ion (R' = H). The availability of the lone pair of the amine nitrogen is also expected to contribute to the stability of this intermediate. On the other hand, if the benzene ring of benzotriazole is suitably substituted with an electron-withdrawing substituent (X and/or Y), then anion (3.3) should become a better leaving group, thus again facilitating the dissociation; on the contrary, substitution with electron donating substituents X or Y should raise the barrier to interconversion (Scheme 3.1).

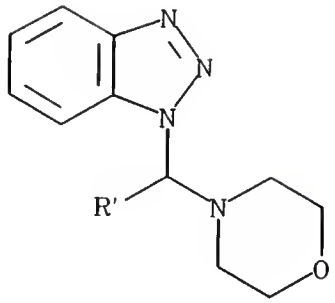
As mentioned in Chapter 2, the size of the substituents NR_2 in the side chain affects the isomeric ratio in the solution. A more pronounced effect is expected if a substituent R' ≠ H is introduced in the structure.

The isomeric ratio was also found to change in different solvents (Chapter 2). A more systematic study is sought here in order to assess the influence of the solvent polarity on the two isomers and on the invoked iminium ion intermediate.

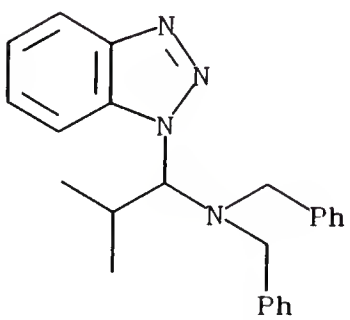
To acquire a more quantitative picture of how the relative energy levels of the 1- and 2- isomers can be changed by manipulating the electronic factors that influence the rearranging part of the molecule, we prepared a series of compounds, namely (3.4-3.15) (Scheme 3.2).



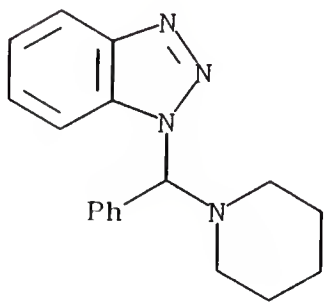
	X	Y	R′
3.4	H	H	H
3.5	NO_2	H	H
3.6	Cl	H	H
3.7	Me	Me	H
3.8	H	H	Pr^i



	R′
3.9	H
3.10	C_6H_5
3.11	C_6H_4-4-NO_2
3.12	C_6H_4-4-OMe
3.13	Pr^i



3.14



3.15

Scheme 3.2

3.2 Results and Discussion

3.2.1 Preparation of Compounds

Adducts of type (3.1), (R' ≠ H) have not been described in the literature except for the adduct prepared from benzaldehyde and dimethylamine [76JCS(P2)741], which was characterized only by a proton NMR spectrum at -30°C. Previous attempts in this group to obtain products of condensation of benzotriazole with aliphatic aldehydes and amines had resulted in complex mixtures [87JCS(P1)799].

Compounds of type (3.1) were successfully prepared from benzotriazole, an aldehyde (aromatic or aliphatic) and a secondary amine by azeotropic removal of water in benzene. Initial attempts to isolate some of these adducts were not very successful. The oily products could not be purified, as distillation and column chromatography results in decomposition and/or hydrolysis of the crude materials. The solid adducts, however, were much easier to handle, since recrystallization was always possible. Methods were eventually worked out for the isolation and complete characterization of the vast majority of compounds (3.1) (R' ≠ H) (see experimental). For most of them, however, the ^{13}C- and ^{1}H-NMR spectra near or at room temperature were much affected by peak broadening coalescence, especially when examined in chloroform solution. This can give the incorrect impression that the compounds are not pure. In general, the most convenient and effective way to handle

adducts (3.1) was to use them directly for synthetic applications without prior purification (see Chapters 4, 5, 6 and 7).

3.2.2 Characterization of Compounds and Assignment of the H-1 and C-13 NMR Spectra

Compounds (3.5), (3.8) and (3.12) were best characterized by low temperature ^{1}H-NMR spectra in a solvent where a large dispersion of chemical shifts was observed and peaks due to the two isomers could be readily detected (see Experimental). All ^{13}C-NMR spectra were recorded in deuterated chloroform. Low temperature ^{13}C-NMR spectra were obtained in the cases of (3.5), (3.8), and (3.15), where broad peaks were observed at room temperature.

As discussed in Chapter 2, all the compounds unsubstituted in the benzene ring of benzotriazole are mixtures of the 1- and 2- isomers and show both benzotriazol-1-yl and benzotriazol-2-yl type substitution patterns in the ^{1}H- and the C-13 NMR spectra. The C-13 spectra of the above compounds were easier to interpret than the ^{1}H-NMR spectra, where frequently considerable overlapping of some benzotriazole protons by signals of R and R' resulted in observation of complex multiplets. In most cases, however, assignment was achieved (see Tables 3.1 - 3.3 and Experimental) using literature information [75JCS(P2)1695], [83H1787].

Two structural features introduced increased complexity in the spectra of some compounds.

(a) Substitution on the C-5 atom of the benzotriazole ring without equivalent substitution at the C-6 position [as in (3.5) and (3.6)], resulted in the generation of three interconverting (1-, 2-, and 3- substituted) isomers in the solutions and consequently complex ^{1}H- and ^{13}C-NMR spectra.

(b) The existence of an asymmetric carbon atom (when $R' \neq H$) caused chemical shift non-equivalency to protons in methylene and methyl groups up to three bonds away. This resulted in complicated ^{1}H-NMR spectra, especially in the compounds bearing aliphatic side chains, but fortunately the C-13 spectra were not affected.

In these cases, additional experiments were carried out to aid the complete assignment as will be discussed next.

Spectral assignment of N-[(5-nitrobenzotriazol-N-yl)-methyl]pyrrolidine (3.5). Chloroform solutions of N-[(5-nitrobenzotriazolyl)methyl]pyrrolidine (3.5) at -25°C contained then 2- and 3- isomers in equal amounts, while the 1-isomer was the major component (at -25°C, [1-]:[2-]:[3-] = 44:28:28). The complete assignment of the ^{1}H- and ^{13}C-NMR spectra of this adduct could be achieved only by preparation of model compounds.

Thus, 5-nitrobenzotriazole was methylated, and the products 1-methyl-, 2-methyl- and 3-methyl-5-nitrobenzotriazole [64T211] were separated by column chromatography. The individual fractions were identified by comparing their melting points to literature values. The least polar

fraction was identified as 2-methyl-5-nitrobenzotriazole (m.p.185-188°C; lit. [64T211] m.p.187°C). The most polar fraction was 1-methyl-5-nitrobenzotriazole (m.p.160-162°C; lit. [64T211] m.p.163°C). Fractional crystallization had been used in the literature to separate the two isomers. Column chromatography, however, of our methylation mixture yielded an additional isomer, of intermediate polarity, which was reasoned to be 3-methyl-5-nitrobenzotriazole, and had not been reported previously [64T211].

The ^{1}H- and ^{13}C-NMR spectra of the individual methylation products were recorded in $CDCl_3$. The spectra of the mixture of the three compounds were then easily assigned, and they showed a very good correspondence to those of (3.5) (see Experimental). Figure 3.1 shows the aromatic proton region of (3.5) as compared to that of the mixture of 1-, 2-, and 3-methyl-5-nitrobenzotriazoles in $CDCl_3$.

Spectral assignment of N-[(5-chlorobenzotriazol-N-yl)]-methyl]pyrrolidine (3.6). In the case of the chloro-compound (3.6), the populations of the three isomers were all significantly different, (20°C, $CDCl_3$, [1-]:[2-]:[3-] = 45:23:32) thus enabling assignment of the ^{13}C-NMR spectrum. The aromatic region of the ^{1}H-NMR spectrum, with a multitude of peaks, was impossible to assign. A two-dimensional proton-carbon correlation spectrum (HETCOR) (Figure 3.2)

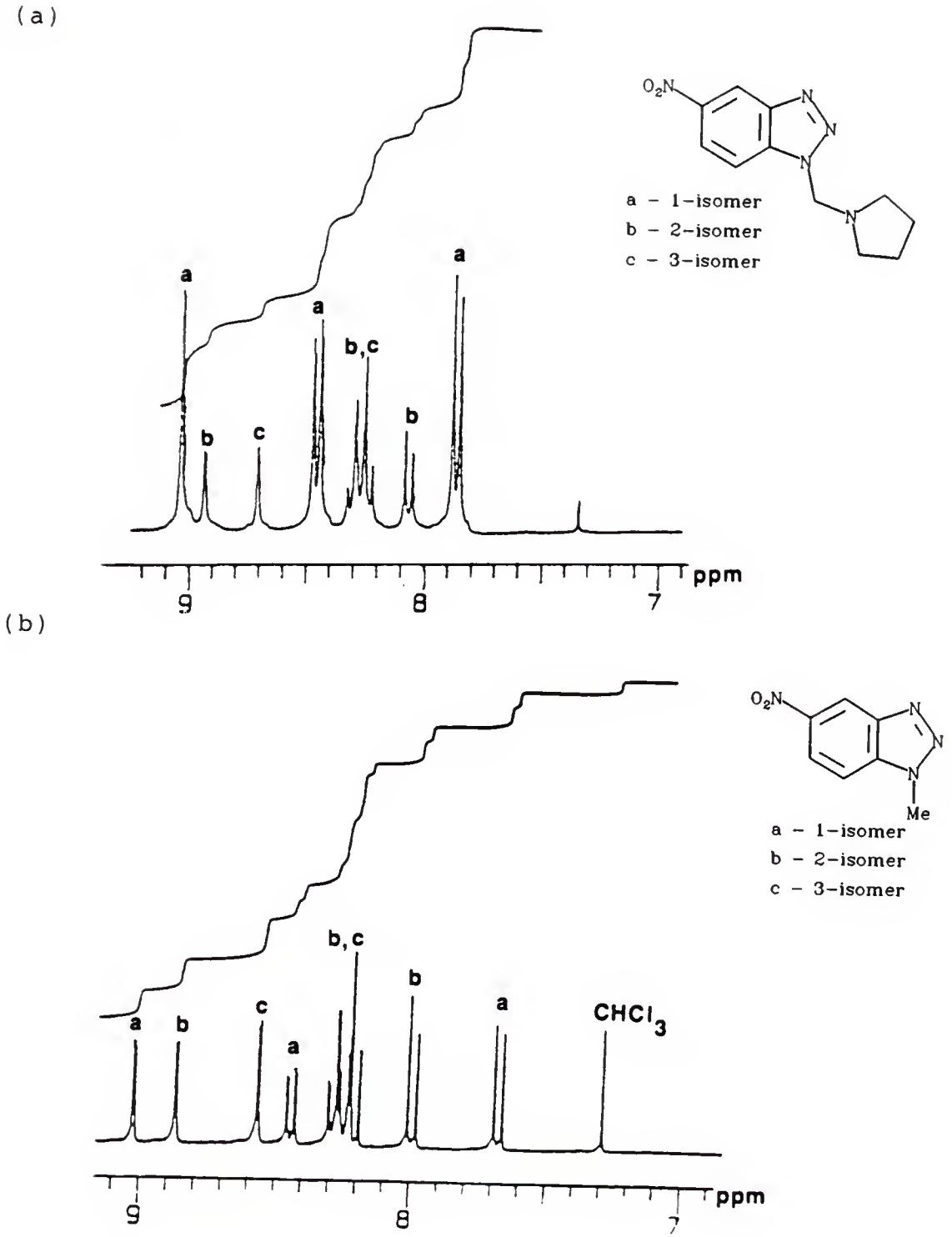


Figure 3.1 Aromatic region of the ^{1}H-NMR spectrum ($CDCl_3$) of (a) N-[(5-nitrobenzotriazol-N-lyl)methyl]pyrrolidine (3.5) (-25°C), and (b) a mixture of 1-, 2- and 3-methyl-5-nitrobenzotriazoles (25°C).

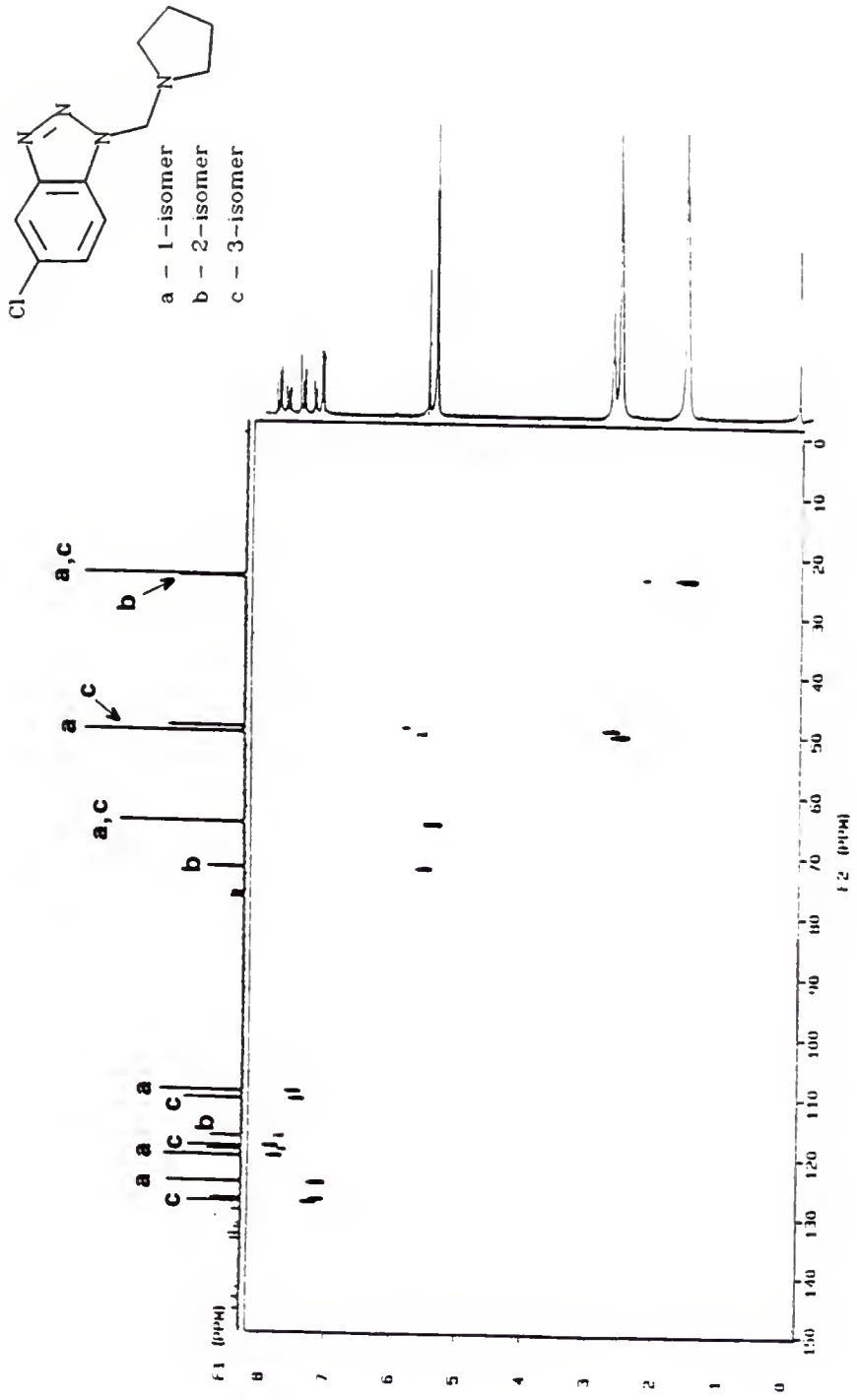


Figure 3.2 A $^{1}H-^{13}C$ correlation spectrum (HETCOR) of N-[(5-chlorobenzotriazol-N-yl)methyl]pyrrolidine (3.6).

helped in assigning each of the aromatic peaks in the ^{1}H-NMR spectrum to the correct isomer. Literature ^{1}H-NMR spectra [79HCA2129] of 1-methyl-, 2-methyl-, and 3-methyl-5-chlorobenzotriazole are in agreement with our assignments.

Spectral assignment of isobutyraldehyde adducts (3.8), (3.13) and (3.14). Adduct (3.14) contained only two isomers, however, both the benzylic methylene and the two methyl groups resonated at different frequencies for each of the two isomers. A proton-proton correlation spectrum (COSY), unraveled the assignment of the aliphatic region in the ^{1}H-NMR spectrum of this molecule (Figure 3.3) and of molecules (3.8) and (3.13) which had similar structure. The aromatic region of (3.14), having signals due to the four different ring protons was too complex, and therefore complete assignment was impossible. However, the assignment of the C-13 spectra did not pose any difficulties.

The ^{1}H-NMR spectra of all adducts are described in the experimental section. The ^{13}C-NMR spectra of the 1-isomers are listed in Table 3.1, of the 2-isomers in Table 3.2, and of the 3-isomers of (3.5) and (3.6) in Table 3.3. ^{1}H-NMR spectra above coalescence were also recorded and are listed in Table 3.7 (see end of this Chapter).

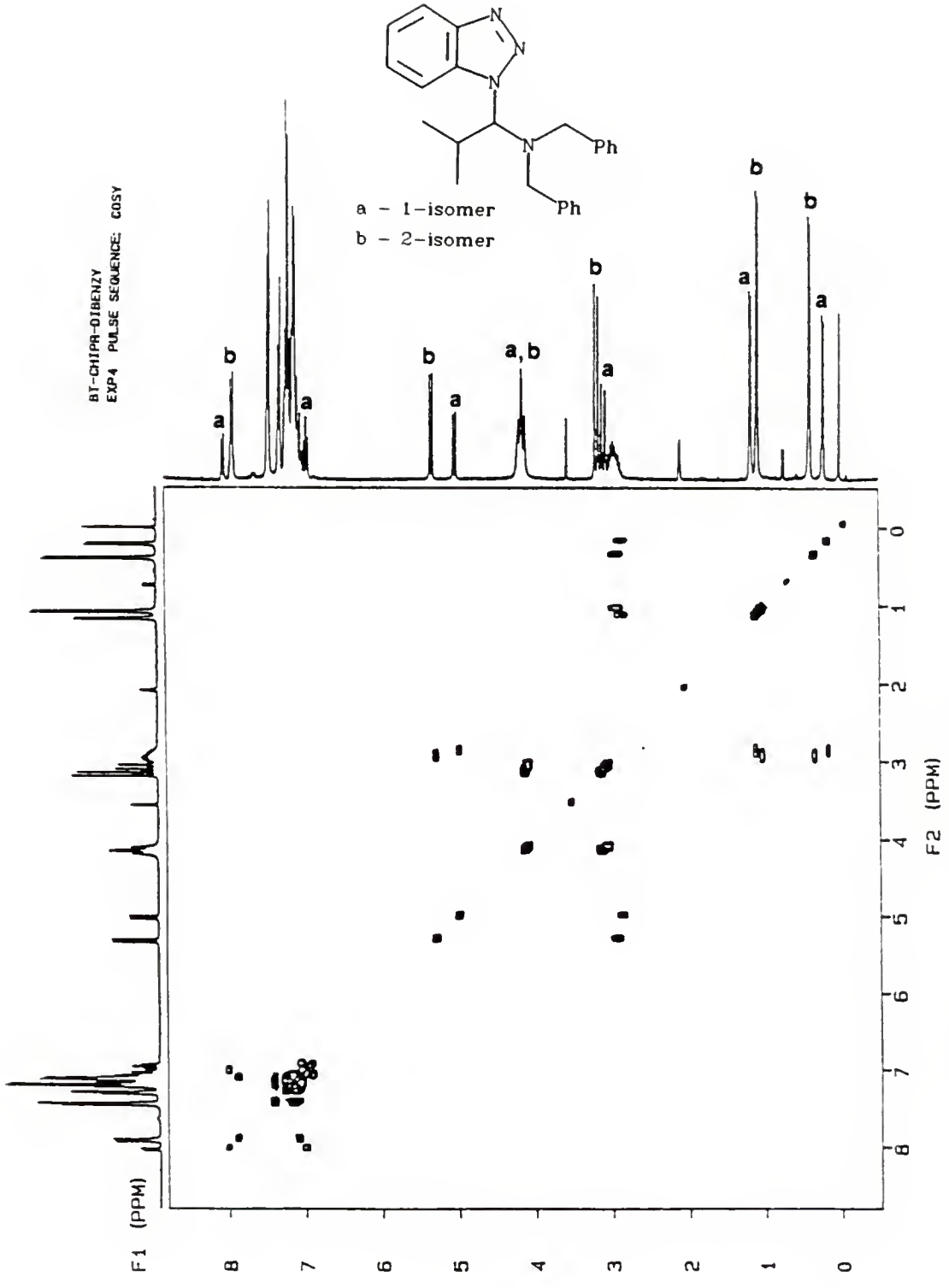


Figure 3.3 A ^{1}H-^{1}H correlation (COSY) spectrum of N-[α-(benzotriazol-N-yl)-β-methyl]propyl-N,N-dibenzylamine (3.14).

Table 3.1. ^{13}C-NMR chemical shifts of the benzotriazol-1-yl isomers, of compounds (3.5a)-(3.15a) at a single temperature (below coalescence) in $CDCl_3$.

No[a]	Tem. (°C)	$-NR_2$	R′	CH	Bt
3.5	-25	49.9 23.4	-[b]	65.5	144.4, 144.2, 136.4[c] 122.8, 116.9, 110.7
3.6	+20	49.9 23.4	-[b]	65.1	145.8,[c] 133.2,[c] 129.1[c] 124.5, 120.1, 109.4
3.8[d]	-48	47.1 22.7	30.5, 19.8 19.0	81.3	144.5, 134.4, 126.9 123.5, 119.2, 109.7
3.9	+20	66.2 50.1	-[b]	68.9	145.5, 133.5, 127.2 123.6, 119.4, 109.6
3.10	+20	66.3 49.6	134.6, 128.4 128.1, 127.2	82.4	145.7, 132.7, 126.9 123.5, 119.6, 111.1
3.11	+20	66.5 49.7	141.9, 142.3 128.7, 123.7	81.1	145.8, 133.0, 127.8 124.2, 120.1, 110.5
3.12	+20	66.4 49.7	159.4, 127.6 113.7, 54.8	82.4	145.6, 132.5, 127.1 123.8, 119.5, 111.4
3.13	+20	66.6 48.8	28.4, 19.7 19.0	85.5	145.0, 134.4, 127.2 123.7, 119.6, 109.7
3.14	+20	138.7 128.9 128.5 127.3 53.4	30.4, 29.6 19.4	80.1	144.9, 135.1, 126.9 123.7, 119.7, 109.8
3.15	-20	50.1 25.4 23.5	134.9, 128.1 128.0, 127.0	82.8	145.4, 132.8, 126.6 123.4, 119.2, 111.5

[a] The complete ^{13}C-NMR spectra of (3.4) and (3.7) were reported in Chapter 2 [see Table 2.2, compounds (2.4) and (2.7)]. [b] R′ = H. [c] The 4° carbon atoms could not be assigned with certainty, therefore peaks could be due to the other isomers. [d] The INEPT pulse sequence at 25 MHz (-48°C, $CDCl_3$) was utilized for unequivocal assignment of the spectrum.

Table 3.2. ^{13}C-NMR chemical shifts of benzotriazol-2-yl isomers of compounds (3.5b)-(3.15b) at a single temperature (below coalescence) in $CDCl_3$.

No[a]	Tem. (°C)	$-NR_2$	R′	CH	Bt
3.5	-25	50.1 23.7	-[b]	73.3	120.5,[c] 119.4, 118.8[d]
3.6	+20	48.9 23.7	-[b]	72.4	145.8,[e] 133.2,[e] 129.1[e] 127.0, 119.0, 116.8
3.8[f]	-48	46.4 22.7	30.5, 19.4	88.7	142.8, 125.8, 117.8
3.9	+20	66.4 59.8	-[b]	76.7	143.8, 126.2, 117.7
3.10	+20	66.7 48.6	135.0, 128.4 128.2, 127.2	88.2	143.5, 126.1, 118.1
3.11	+20	66.6 48.6	147.9, 128.7 123.4	87.2	143.9, 126.8, 118.3
3.12	+20	66.1 48.8	159.4, 126.6 113.9, 54.8	88.1	142.0, 125.2, 114.6
3.13	+20	66.8 48.3	28.4, 19.1 18.9	92.3	143.3, 125.9, 118.0
3.14	+20	138.8 128.5 128.3 127.3 53.3	30.4, 20.0 19.3	87.3	143.5, 126.0, 118.4
3.15	-20	49.4 25.4 23.5	134.9, 128.1 128.0, 127.0	89.0	143.3, 125.9, 117.9

[a] The complete C-13 NMR spectra of (3.4) and (3.7) were reported in Chapter 2 [see Table 2.2, compounds (2.4) and (2.7)]. [b] R′ = H. [c] Assignments can be interchanged with the corresponding atoms of the 1-isomer. [d] The 4° carbon atoms were not detected. [e] The 4° carbon atoms could not be assigned with certainty, therefore peaks could be due to the other isomers. [f] The INEPT pulse sequence at 25 MHz (-48°C, $CDCl_3$) was utilized for unequivocal assignment of the spectrum.

Table 3.3. ^{13}C-NMR chemical shifts of benzotriazol-3-yl isomers of compounds (3.5) and (3.6) at a single temperature (below coalescence) in $CDCl_3$.

No	Tem. (°C)	$-NR_2$	R′	CH	Bt
3.5	-25	49.0 23.4	-[a]	65.9	120.5,[b] 116.4, 107.4
3.6	+20	49.8 23.4	-[a]	65.1	143.8,[c] 134.0,[c] 132.1[c] 127.7, 118.4, 110.6

[a] R′ = H. [b] The quaternary atoms were not detected.

[c] Assignments can be interchanged between corresponding 4° carbon atoms of the 2-isomer; unambiguous assignment of the quaternary carbon atoms could not be made, because a two-dimensional correlation was not possible.

3.2.3 Calculation of Equilibrium Constants (K) and Free Energies (ΔG°) for Isomerization

The equilibrium constants were measured for each compound in several solvents, at the temperatures specified in Table 3.4 (see also footnotes), by integrating the areas of each of the isomers in the ^{1}H-NMR spectra. Positions 1 and 3 of the benzotriazole ring are degenerate [except for adducts (3.5) and (3.6)], and this was taken into account when calculating the populations of the 1-isomers. The free energies of the isomerization process were then calculated from the equation $\Delta G° = -RT\ln K$, where $K = P_1/P_2$ (Table 3.4). The populations P_n were determined from the integration of the N-C<u>H</u>(R)-N proton signals or from the aromatic region of each of the isomers. For adducts (3.5) and (3.6), in

Table 3.4 Equilibrium constants (K) and free energies for the isomerization ($\Delta G°$) of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines (3.4) and (3.7)-(3.15).

No	NR_2 [a]	R′	X	Y	Solvent	T [b] (°C)	K [c]	$\Delta G°$ [d] (kcal/mol)
3.4	Pyr	H	H	H	$CDBr_3$	+22	1.6	-0.25
					CD_3CN	+22	6.2	-1.05
3.7	Pyr	H	Me	Me	$CDBr_3$	+23	1.7	-0.30
					CD_3CN	+22	4.9	-0.95
3.8	Pyr	Pr^i	H	H	Toluene-d_8	-40	0.4	+0.40
					CD_3CN	[e]	[e]	[e]
3.9	Mor	H	H	H	$CDBr_3$	+22	1.8	-0.35
					CD_3CN	+23	5.6	-1.00
3.10	Mor	Ph	H	H	$CDBr_3$	+23	1.2	-0.10
					CD_3CN	+20	2.5	-0.55
3.11	Mor	4-NO_2-C_6H_4	H	H	CD_3CN	+20	2.5	-0.55
3.12	Mor	4-MeO-C_6H_4	H	H	CD_3CN	-20	2.7	-0.50
3.13	Mor	Pr^i	H	H	Toluene-d_8	+25	0.4	+0.55
					$CDCl_3$	+21	0.5	+0.40
					CD_3CN	+23	1.1	-0.05
3.14	Dib	Pr^i	H	H	Toluene-d_8	+25	0.4	+0.55
					$CDBr_3$	+22	0.7	+0.20
					$CDCl_3$	+22	0.8	+0.15
					CD_3CN	+22	0.9	+0.05
3.15	Pip	Ph	H	H	Toluene-d_8	+21	1.1	-0.05
					CD_3CN	[e]	[e]	[e]

[a] Pyr = pyrrolidine; Mor = morpholine; Dib = Dibenzylamine; Pip = Piperidine. [b] Temperature at which the equilibrium constant was measured. [c] $K = P_1 / P_2$, where P_1 and P_2 are the populations of the 1- and 2- isomers, respectively (estimated error ±0.2). [d] Estimated error ±0.05-0.10 kcal/mole.
[e] Signals of two isomers too close to allow reliable measurement of K.

solutions of which a 3-substituted isomer is also present, when separation of the signals allowed, in addition to K = P_1/P_2, K′ = P_3/P_2, and K" = P_1/P_3 could also be calculated. The values so obtained are collected in Table 3.5 (see also footnotes).

A negative ΔG° value indicates that the 1-isomer is more stable than the 2-isomer, while a positive ΔG° shows the reverse. Deuterated acetonitrile was found suitable in obtaining reliable isomeric ratios for nearly all compounds, therefore direct comparison of the obtained ΔG° values could be made, although the temperatures at which equilibrium constants were measured varied (Tables 3.4, 3.5). In general, in solutions of compounds of type (3.1) [R′ = H, i.e (3.4)-(3.7) and (3.9)], the 1-isomer is the most thermodynamically favored component in the mixture.

Table 3.5. Equilibrium constants and free energies for the isomerization of N-[(5-nitro and 5-chlorobenzotriazol-N-yl)-methyl]pyrrolidines (3.5) and (3.6), respectively.

No	NR_2[a]	R′	X	Y	Solv.	T (°C)	K[b]	K′	K"	ΔG°	ΔG°′	ΔG°" (kcal/mol)
3.5	Pyr	H	NO_2	H	Tol-d_8[c]	+21	1.1	-	-	0.05	-	-
					$CDCl_3$	-25	2.5	1.0	2.5	-0.45	0.0	-0.45
					CD_3CN	-48	5.6	2.3	3.0	-0.75	-0.35	-0.50
3.6	Pyr	H	Cl	H	$CDCl_3$	+21	2.0	1.4	1.4	-0.40	-0.20	-0.20
					CD_3CN	-20	6.4	5.5	1.3	-0.95	-0.85	-0.15

[a] Pyr = pyrrolidine. [b] $K = P_1/P_2$, $K' = P_3/P_2$, $K'' = P_1/P_3$, $\Delta G°_n = -RT \ln K_n$ (in kcal/mole). [c] The signals due to the 1- and 3- isomers resonated at the same frequency, therefore $K = [P_1 + P_3]/P_2$.

Adducts of type (3.1) (R′ ≠ H), either show little preference toward either isomer in a common NMR solvent [e.g (3.10) in $CDBr_3$)], or, in extreme cases of steric hindrance, the 2-isomer clearly becomes the most stable [e.g. (3.14) in $CDBr_3$)]; in these cases, K < 1 and $\Delta G^\circ > 0$. Increasing solvent polarity can move the equilibrium toward the 1-isomer, as will be discussed next.

Effect of the solvent. Polar solvents have been shown (Chapter 2) [75JCS(P1)1181] to favor the 1-isomer in solutions of compounds of type (3.1) (R′ = H). Dipole moment measurements of simple 1-substituted benzotriazole derivatives [50CR1], [61MI1], [75BSF1675], indicate that (somewhat surprisingly) they are more polar than their 2-substituted isomers:

R-benzotriazole	μ (D, 25°C, in C_6H_6)
1-Methyl	3.95
2-Methyl	0.49
1-Phenyl	4.08
2-Phenyl	0.97

Here we observe a similar effect. For example, the ΔG° value of (3.14) indicates that the 1-isomer becomes more favored on going from toluene (μ = 0.36 D) [85MI1] to bromoform (μ = 0.99 D) to acetonitrile (μ = 3.92), with chloroform (μ = 1.01 D) in an intermediate position. A very marked effect is observed in acetonitrile solutions of (3.4)-(3.8), and (3.9), where the 1-isomer has increased to

more than 83% in the equilibrium mixture. Compound (**3.13**) exemplifies a case in which solvent polarity can determine which isomer will predominate in the solution (2-isomer in toluene-d_8; 1-isomer in acetonitrile-d_3).

Effect of substituents R and R'. Increased bulkiness of R' results in increased amounts of the 2-isomer in the equilibrium mixture. This is reflected by a decreasing magnitude of K in acetonitrile on going, for example, from (**3.9**) to (**3.13**). When R' is a phenyl or a p-substituted phenyl group, the equilibrium constant is often close to unity [e.g. (**3.10**) in $CDBr_3$, (**3.15**) in toluene-d_8], meaning that no actual preference is expressed for either of the two isomers in the particular solvent. The results in Table 3.4 indicated that the peri-interactions (buttressing between H-7 and the aminoalkyl substituent) are rather important [75JCS(P2)1695] in the 1-isomer. This was further demonstrated by a different experiment: the ^{1}H-NMR spectrum of the pyrrolidine-isobutyraldehyde adduct (3.8) in toluene-d_8, showed that the benzotriazole H-7 and methine NC<u>H</u>N signals of the 1-isomer became broad and moved toward each other as the temperature was lowered from -20°C to -80°C. Restricted rotation about the Bt-CHR'NR_2 bond was evidently responsible for this phenomenon, which was observed only for the 1-isomer (Figure 3.4).

The electron-withdrawing or electron-releasing nature of the substituents R and R' does not seem to have any noticeable effect, as the magnitude of $\Delta G°$ remains the same

(within experimental error) for (3.10) and (3.11) in acetonitrile-d_3, and for (3.8), (3.13) and (3.14) in toluene-d_8, while the differences observed in (3.15) and (3.8) in toluene-d_8 would rather be attributed to steric effects.

Effect of substituents X and Y. The 5-nitro- (3.5) and 5-chloro- substituted (3.6) compounds, each contain three interconverting isomers in their solutions, occupying different energy minima, as reflected by different $\Delta G°$ values for each isomerization process (Table 3.5). The 1-isomer is again the predominant and the 2-isomer the least abundant, in both cases and all solvents studied.

Literature information on the polarity of 5-nitro- [64T211] and 5-chloro- [79HCA2129] methylbenzotriazoles, was combined with our observations (see Experimental), deduced from the order of elution of these compounds from column chromatography (silica gel), ranks them, according to increasing polarity:

2-Me-5-NO_2-Bt < 3-Me-5-NO_2-Bt <1-Me-5-NO_2, and

2-Me-5-Cl-Bt < 1-Me-5-Cl-Bt < 3-Me-5-Cl-Bt.

By analogy, the polarity of isomeric compounds in each of (3.5) and (3.6), is expected to follow the same order. This is verified by the magnitude of the K values observed for (3.5). However, K values for (3.6) show that the 1-isomer is more polar than the 3-isomer, which is in contrast to the literature report.

3.2.4 Variable Temperature NMR Spectral Study: Calculation of Free Energies of Activation ($\Delta G^{\ddagger}$)

The temperatures at which the characteristic proton resonances of the 1- and 2- isomers coalesced were measured. Specifically, the signals of the methylene groups, located between the amino and the benzotriazole nitrogen atoms, of the two isomers, were monitored for compounds (3.4)-(3.7) and (3.9). The corresponding methinic proton signals were monitored for compounds (3.8) and (3.10)-(3.15). The ranges of temperatures within which coalescence occurred were visually estimated from the lineshape of the signals under observation, and are listed in Table 3.6. Figure 3.4 shows the temperature dependence of the ^{1}H-NMR spectrum of (3.8) in deuterated toluene. The doublets of the two isomers slowly coalesce to a single broad peak at 5.3 ppm. The other broad signal at about 6.3 ppm originates from the aromatic region and its assignment is uncertain.

Approximate free energies of activation [74MI1], [80MI2], [82MI1] were calculated using the simplified equation,

$$\Delta G^{\ddagger} = RT_c[22.96 + \ln(T_c/\delta\nu)]$$

where T_c is the coalescence temperature (in °K) and $\delta\nu$ the chemical shift difference (in Hz) of the two separate peaks in the slow exchange region. The error in T_c is ± 2 to ± 3°C, and this corresponds to ± 0.1 to ± 0.2 kcal/mole in $\Delta G^{\ddagger}$ [74MI1]. The 1- to 2-isomerization process is intermolecular (Chapter 2) and the populations of the isomers are

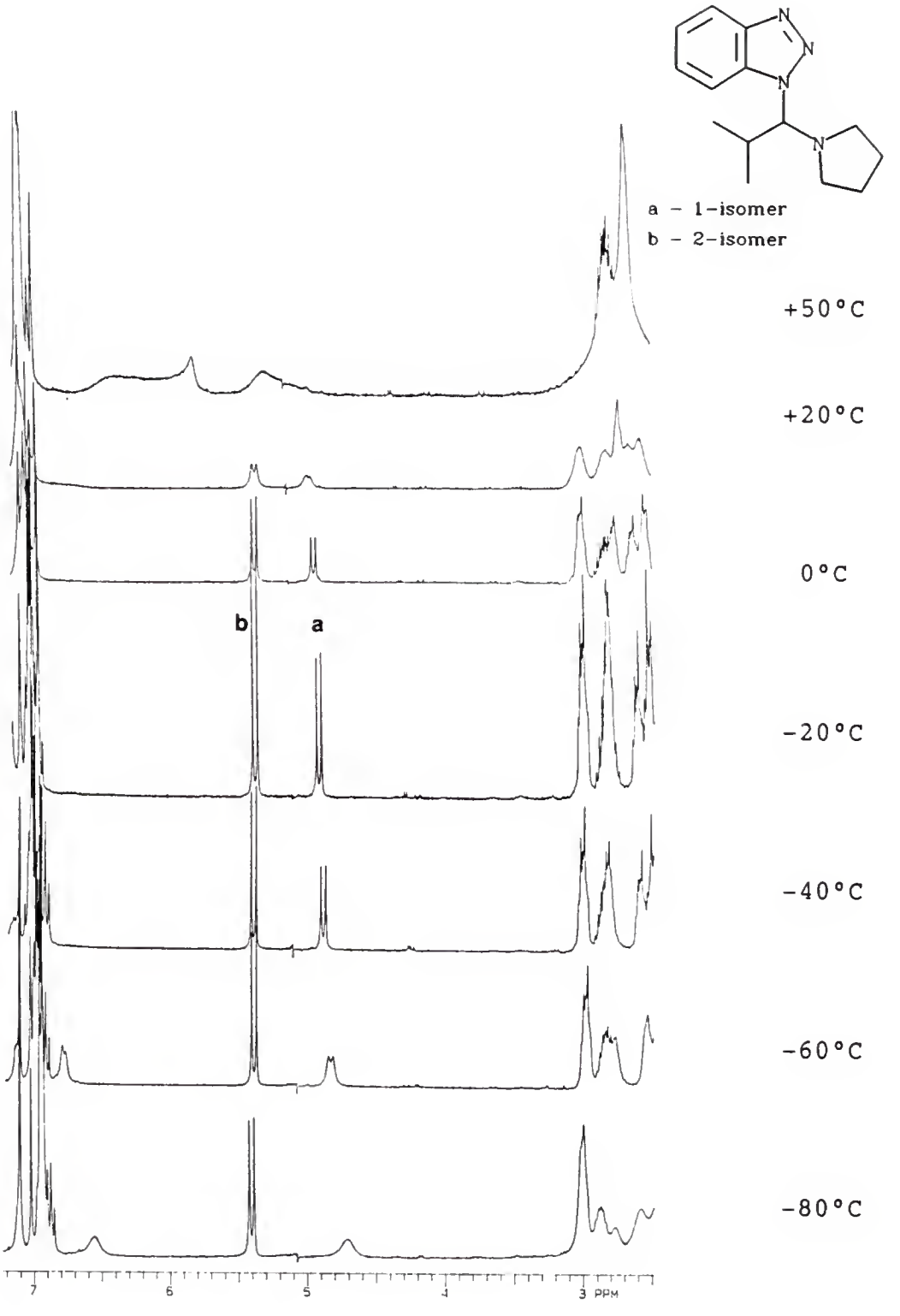


Figure 3.4 Temperature dependence of the ^{1}H-NMR spectrum [NC$\underline{H}$(Pr^{i})N region] of adduct (**3.8**) in toluene-d_8.

unequal in most cases studied, therefore additional error is introduced in the calculations [82MI1]. However, since only approximate $\Delta G^{\ddagger}$ values are desired for evaluation of the relative ease of isomerization of the compounds, the free energies of activation listed in Table 3.6 give satisfactory indication. The activation energies, calculated from the equation mentioned above, represent the barrier to conversion of the least to the most stable isomer. Thus, the calculated $\Delta G^{\ddagger}$ values for compounds with $\Delta G^{\circ} < 0$ pertain to the 2- to 1- isomerization, whereas for those with $\Delta G^{\circ} > 0$ pertain to the reverse. However the numbers in Table 3.6 for (**3.8**) and (**3.14**) have been adjusted so that all pertain to 2- to 1- conversion.

The choice of a suitable solvent for VT work is not always easy [88JOC2629]. Both low and high temperature spectra were obtained in deuterated toluene, but for most compounds coalescence did not occur below the boiling point of this solvent. Coalescence was obtained in the higher boiling solvent, bromoform-d (b.p. 150°C), but the $\Delta G^{\ddagger}$ values were generally lower in $CDBr_3$ than in toluene-d_8, due to solvent polarity effects. In cases where the proton resonances under observation were not well resolved or obscured by other signals in the above solvents, [e.g (**3.11**), (**3.12**)], deuterated acetonitrile was used but this could not be extended to all molecules: the amount of the 2- isomer in (**3.4**) and (**3.7**) and (3.9) in CD_3CN was very small (see Table 3.4), resulting in very weak proton resonances, and therefore unacceptable errors in the measurement of T_c.

Table 3.6 Free energies of activation for the isomerization of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines (3.4)-(3.15).

No	NR_2[a]	R′	X	Y	Solvent	T[b] (°C)	$\Delta G^{\ddagger}$[c] (kcal/mol)
3.4	Pyr	H	H	H	$CDBr_3$	85	18.2
3.5	Pyr		NO_2	H	Toluene-d_8	105	18.0
					Benzene-d_6	63	16.0
					$CDCl_3$	32	15.4
3.6	Pyr	H	Cl	H	$CDBr_3$	66	17.0
3.7	Pyr	H	Me	Me	$CDBr_3$	98	18.7
3.8	Pyr	Pr^i	H	H	Toluene-d_8	48	15.6
3.9	Mor	H	H	H	$CDBr_3$	86	18.3
3.10	Mor	Ph	H	H	$CDBr_3$	62	17.7
					CD_3CN	63	16.9
3.11	Mor	4-NO_2-C_6H_4	H	H	CD_3CN	83	18.6
3.12	Mor	4-MeO-C_6H_4	H	H	CD_3CN	35	15.7
3.13	Mor	Pr^i	H	H	CD_3CN	35	16.1
3.14	Dib	Pr^i	H	H	$CDBr_3$	75	17.9
3.15	Pip	Ph	H	H	Toluene-d_8	73	16.8

[a] Pyr = pyrrolidine; Mor = morpholine; Dib = Dibenzylamine; Pip = Piperidine. [b] ±2°C. [c] ±0.15 kcal/mol

Effect of the solvent. The nature of the solvent affects the magnitudes of both $\Delta G^{\ddagger}$ and $\Delta G°$. Table 3.6 clearly shows that the energy barrier is highest in toluene-d_8, intermediate in bromoform-d, and lowest in acetonitrile-d_3. This is as expected, because a more polar solvent

provides more stabilization to the ion pair [(3.2) + (3.3)] than to the individual isomers (Scheme 3.1), thus lowering the energy difference between the ion pair and either of the isomers.

Effect of R'. The results in Table 3.6 clearly show that the free energy of activation is lower when resonance stabilization is provided to the intermediate (3.2) through the substituent R' (Scheme 3.1), compared to the unsubstituted cases. Specifically, in acetonitrile, the order of decreasing $\Delta G^{\ddagger}$ values is (3.11) > (3.10) > (3.12). Strong stabilization to the electron deficient iminic carbon is also provided by isopropyl substituents, as indicated in the case of (3.8) vs (3.4), and to a lesser extent, (3.13) vs (3.9).

Effect of substituents in the benzotriazole ring. The electron-withdrawing nitro substituent of (3.5) stabilizes the negative charge developed on anion (3.3), and therefore facilitates N-$CHNR_2$ bond dissociation leading to recombination on the N-2 atom of benzotriazole. The electron-donating methyl groups of (3.7) have the opposite effect, raising the energy barrier to a relatively high value. The 5-chloro substituent is intermediate. The calculated $\Delta G^{\ddagger}$ values in $CDBr_3$ are therefore classified in order of decreasing magnitude, as follows: (3.7) > (3.4) > (3.6) > (3.5). Compound (3.5) in $CDBr_3$ is very near coalescence at

room temperature, so the $\Delta G^{\ddagger}$ in this solvent could not be measured (the solvent freezes at +8.3°C), but the corresponding value in chloroform-d suggests it will be less than 15.4 kcal/mol.

For compounds (3.5) and (3.6) one coalescence temperature was observed. The NCH_2N protons of the 1- and 3- isomers of the nitro adduct (3.5) resonated at the same frequency, while the singlet of the 2-isomer emerged at 0.4 ppm downfield, in both toluene-d_8 and benzene-d_6. The two peaks coalesced into one as the temperature increased. In $CDCl_3$ solution, however, three separate peaks were observed for each isomer. The $NC\underline{H}_2N$ singlets due to 1- and 3- isomers were very close, and they overlapped very soon with a moderate increase in temperature, whereas true coalescence came later at a higher temperature. Similar behavior was demonstrated by (3.6).

Effect of the nature of secondary amine. The availability of the lone pair of electrons on the amine nitrogen for donation to the adjacent electron-deficient carbon in adducts of type (3.1), plays a significant role in determining the height of the barrier. This is best illustrated by the compounds bearing the isopropyl substituent, where a significant amount of positive charge could be developed on the $N\underline{C}HCHMe_2$ atom. We then observe, in order of decreasing $\Delta G^{\ddagger}$ magnitude, (3.10) > (3.15), and (3.14) > (3.8). The order of decreasing $\Delta G^{\ddagger}$ values bears an

inverse correlation with the pK_a values of the corresponding secondary amines [72MI1]. Thus, pK_a[(morpholine) = 8.49] < pK_a[(piperidine) = 11.20] and again pK_a(dibenzylamine) = 8.52 < pK_a[(pyrrolidine) = 11.30]. The benzotriazole adducts of morpholine are consequently more easily isolable and stable compounds than the adducts of pyrrolidine or piperidine, most of which are readily hydrolyzed oils or low melting solids.

3.3 Conclusions

The free energy of activation for the benzotriazol-1-yl to benzotriazol-2-yl rearrangement of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines, is greatly dependent on the degree of stabilization provided to either of the intermediate ions (3.2) or (3.3): the greater the stabilization the lower the energy barrier. The greater the polarity of the solvent the lower the value of $\Delta G^{\ddagger}$. Finally, the bulkier the dialkylaminoalkyl- or aryl- substituent the more abundant the 2-isomer, which in extreme cases becomes the predominent component, as shown by values of of $K < 1$ and $\Delta G^{\circ} > 0$.

The chemical reactivity of the compounds studied can therefore be tailored according to the appropriate substitution. Compounds for which $\Delta G^{\ddagger}$ is low, react rapidly and cleanly with weak nucleophiles such as amines with concurrent removal of benzotriazole. Compounds having high $\Delta G^{\ddagger}$ values are much less reactive toward the same

nucleophiles. The following Chapters, and in particular Chapter 7, demonstrate results due to the enhanced reactivity of benzotriazole adducts (3.1) in detail.

3.4 Experimental

3.4.1 Methods and Reagents

^{1}H-NMR spectra were recorded on a Varian VXR 300 MHz instrument using TMS as the internal reference and as a standard peak for linewidth comparisons. The samples were solutions of 50-70 mg of compound in 0.55 ml of solvent, in 5 mm nmr tubes. The temperature was raised in 10°C increments allowing at least 10 min for equilibration at each setting. High temperature calibration of the instrument with an ethylene glycol standard sample, showed that the set and actual temperatures were in agreement within ±1°C. Variable temperature measurements were repeated twice and equilibrium constant values were the average of at least three measurements.

Deuterated solvents were purchased from MSD Isotopes (toluene-d_8, $CDCl_3$, C_6D_6, CD_3CN) and Chemalog ($CDBr_3$) and were used directly. ^{13}C-NMR spectra were recorded on either a JEOL-FX 100 (25 MHz, FT mode) or a Varian XL 200 (50 MHz), or a Varian VXR 300 (75 MHz) instrument. Two-dimensional spectra were recorded on the VXR 300 spectrometer using the standard software for COSY and HETCOR pulse sequences provided by Varian.

Reagents and miscellaneous preparative and chromatographic methods are described in Chapter 4.

3.4.2 Preparation of N-[(Benzotriazol-N-yl)methyl]-N,N-dialkylamines

The preparation of the following compounds has been described in Chapter 2: N-[(benzotriazol-N-yl)methyl]-pyrrolidine (**3.4**), and N-[(5,6-dimethylbenzotriazo-N-lyl)-methyl]pyrrolidine (**3.7**) [see preparation of compounds (**2.4**) and (**2.7**), respectively].

N-[(5-Nitrobenzotriazol-N-yl)methyl]pyrrolidine (**3.5**). 5-Nitrobenzotriazole (5.42 g, 0.033 mol), pyrrolidine (0.038 mol, 3.1 ml), and 37% aq. formaldehyde (0.04 mol, 3.4 ml) were stirred in methanol according to the standard literature procedure [75JCS(P1)1181] (see also Chapter 2). Following evaporation of the solvent the compound was at first obtained as an oil, which then solidified gradually after stirring with diethyl ether in a dry ice/acetone bath. N-[(5-Nitrobenzotriazol-N-yl)methyl]pyrrolidine was collected as a yellow solid (7.22 g, 88.5%), m.p. 76-78°C (from diethyl ether) (Found, C, 53.01; H, 5.14; N, 28.21%. $C_{11}H_{13}N_5O_2$ requires, C, 53.44; H, 5.30; N, 28.32%); δ_H ($CDCl_3$, -25°C) 1-isomer, 9.04 (d, J = 2 Hz, H-4), 8.46 (dd, J = 9 Hz, J = 2 Hz, H-6), 7.88 (d, J = 9 Hz, H-7), 5.76 (s, NCH_2N), 2.78 (br s, $NC\underline{H}_2CH_2$), 1.80 (br s, $NCH_2C\underline{H}_2$); 2-isomer, 8.94 (d, J = 2 Hz, H-4), 8.32 (dd, J = 9 Hz, J = 2

Hz, H-6), 8.08 (d, J = 9 Hz, H-7), 5.85 (s, NCH_2N), 2.87 (br s, $NC\underline{H}_2CH_2$), 1.80 (br s, $NCH_2C\underline{H}_2$); 3-isomer, 8.71 (d, J = 2 Hz, H-4), 8.28 (dd, J = 9 Hz, J = 2 Hz, H-6), 8.25 (d, J = 9 Hz, H-7), 5.78 (s, NCH_2N), 2.78 (br, s, $NC\underline{H}_2CH_2$), 1.80 (br s, $NCH_2C\underline{H}_2$).

N-[(5-Chlorobenzotriazol-N-yl)methyl]pyrrolidine (3.6). It was prepared as (3.5), using the same molar amounts of the required starting materials. The oily residue remained after evaporation of the solvent soon started crystallizing. N-[(5-Chlorobenzotriazol-N-yl)methyl]pyrrolidine was obtained as an off-white solid (5.75 g, 71%), m.p. 58-60°C (from diethyl ether/hexanes (7:1, v/v) (Found, C, 55.57; H, 5.40; N, 23.82%. $C_{11}H_{13}ClN_4$ requires, C, 55.82; H, 5.54; N, 23.67%); δ_H ($CDCl_3$, +21°C) 1-isomer, 7.96 (d, J = 9 Hz, H-7), 7.45 (d, J = 2 Hz, H-4), 7.31 (d, J = 9 Hz, H-6, overlaps with same proton of other isomer), 5.54 (s, NCH_2N), 2.74 (br m, $NC\underline{H}_2CH_2$), 1.73 (m, $NCH_2C\underline{H}_2$); 2-isomer, 7.87 (d, J = 2 Hz, H-4), 7.82 (d, J = 9 Hz, H-6), 7.31 (d, J = 9 Hz, H-7), 5.68 (s, NCH_2N), 2.85 (br m, $NC\underline{H}_2CH_2$), 1.73 (m, $CH_2C\underline{H}_2$); 3-isomer, 8.02 (d, J = 2 Hz, H-4), 7.59 (d, J = 9 Hz, H-7), 7.43 (dd, J = 9 Hz, J = 2 Hz, H-6), 5.57 (s, NCH_2N), 2.74 (br m, $C\underline{H}_2CH_2$), 1.73 (m, $NCH_2C\underline{H}_2$).

N-[(Benzotriazol-N-yl)methyl]morpholine (3.9). The compound was prepared according to the general literature method [52JA3868] (see also Chapter 2), and was obtained as a white solid (95%), m.p. 108-109.5°C (from 95% ethanol);

lit. [52JA3868] m.p. 104-105°C; δ_H ($CDCl_3$) 1-isomer, 8.06 (dd, J = 8 Hz, J = 1 Hz, H-4), 7.48 (td, J = 8 Hz, J = 1 Hz, H-5 or H-6), 7.37 (m, H-7, H-6 or H-5), 5.41 (s, NCH_2N), 3.65 (m, OCH_2), 2.6 (m, CH_2N); 2-isomer, 7.88 (AA' m, J = 6.5 Hz, H-4, H-7), 7.37 (BB' m, H-5, H-6, partially overlapping with signals of 1-isomer), 5.53 (s, NCH_2N), 3.65 (m, OCH_2), 2.69 (m, CH_2N).

3.4.3 Preparation of N-[α-(Benzotriazol-N-yl)alkyl]-N,N-dialkylamines

General method. Benzotriazole (7.942 g, 0.0667 mol) and a secondary amine (1 equiv.) were stirred in dry benzene (50 ml) and then the aldehyde (1 equiv.) was added. The mixture was heated under reflux in a Dean-Stark apparatus, until the theoretically calculated amount of water (~ 1.2 ml) had been collected (1-5 days). Isolation and purification is described below for each compound.

N-[α-(Benzotriazol-N-yl)-β-methyl)propyl]pyrrolidine (3.8). The solvent was evaporated at room temperature under reduced pressure (0.2 mm Hg), and the resulting oil was triturated with petroleum ether/diethyl ether in a dry ice/acetone bath. N-[α-(Benzotriazol-N-yl)-β-methyl)-propyl]pyrrolidine was obtained as a beige solid (41%), which was dried under vacuum (0.2 mm Hg, 2 days); m.p. 50-53°C (Found, C, 67.93; H, 7.95%. $C_{14}H_{20}N_4$ requires, C, 68.82; H, 8.25; N, 22.93%); δ_H (toluene-d_8, -20°C) 1-isomer, 7.99 (d, J = 9 Hz, H-4), 7.02 (m, H-5,6,7), 4.92

(d, J = 10 Hz, NC$\underline{H}$N), 3.01 (m, C$\underline{H}$Me$_2$), 2.85 (m, NC$\underline{H}_2$CH$_2$), 2.23 (m, NCH$_2$C$\underline{H}_2$), 1.06 (d, J = 10 Hz, CH$_3$), 0.44 (d, CH$_3$); 2-isomer, 7.87 (AA' m, J = 6.5 Hz, H-4, H-7), 7.37 (BB' m, H-5,6 and protons of other isomer), 5.38 (d, J = 10 Hz, NCHN), 3.02 (m, C$\underline{H}$Me$_2$), 2.56 (m, NC$\underline{H}_2$CH$_2$), 2.23 (m, CH$_2$C$\underline{H}_2$), 1.04 (d, J = 10 Hz, CH$_3$), 0.56 (m, J = 10 Hz, CH$_3$).

N-[α-(Benzotriazol-N-yl)benzyl]morpholine (3.10). Cooling of the hot benzene solution resulted in precipitation of a solid, which was thinned with diethyl ether in a cold bath and filtered. N-[α-(Benzotriazol-N-yl)benzyl]morpholine was collected as a white powder (87%), m.p. 110-112°C (from benzene) (Found, C, 69.01; H, 6.19; H, 19.00%. $C_{17}H_{18}N_4O$ requires, C, 69.37; H, 6.16; N, 19.03%); δ_H (C_6D_6, +21°C) 1-isomer, 8.03 (dd, J = 8 Hz, J = 1 Hz, H-4), 7.26 (m, H-5,6 and protons of Ph groups), 7.05 (m, Ph), 6.45 (s, NCHN), 3.42 (m, OCH$_2$), 2.29 (m, CH$_2$N, superimposed on signals of other isomer); 2-isomer, 7.89 (AA' m, J = 3 Hz, H-4, H-7), 7.26 (BB' m, H-5,6 and Ph protons), 7.05 (m, Ph), 6.78 (s, NCHN), 3.44 (m, OCH$_2$), 2.69 (m, CH$_2$N).

N-[α-(Benzotriazol-N-yl)-α-(4-nitrophenyl)methyl]-morpholine (3.11). The product was obtained as a hard yellowish solid (21.5 g, 96%) m.p. 145-148°C (from 95% ethanol) (Found, C, 60.35; H, 5.03; N, 20.50%. $C_{17}H_{17}N_5O_3$

requires, C, 60.17; H, 5.05; N, 20.64%); δ_H ($CDCl_3$, +21°C) 1-isomer, 8.22 (d, J = 8 Hz, NO_2-CC_2H_2, overlapping with corresponding signals of other isomer), 8.13 (dd, J = 8 Hz, J = 1 Hz, H-4), 7.63 (d, J = 8 Hz, $NO_2CC_2H_2C_2\underline{H}_2$), 7.52-7.35 (m, H-5,6 overlapping with signals of other isomer), 6.79 (s, NCHN), 3.77 (m, OCH_2), 2.64 (m, CH_2N); 2-isomer, 8.21 (d, $NO_2CC_2H_2$, overlapping with 1-isomer), 7.93 (AA' m, J = 3 Hz, H-4,7), 7.52-7.35 (BB' m, H-5,6 and protons of 1-isomer), 6.85 (s, NCHN), 3.64 (m, OCH_2), 2.85 (m, CH_2N).

N-[α-(Benzotriazol-N-yl)-α-(4-methoxyphenyl)methyl]-morpholine (3.12). The product was a low melting (m.p. less than 20°C) solid, which could not be purified (remained as a very viscous oil) and was characterized by ^{1}H- (see below), and ^{13}C-NMR spectra at -20°C (see Tables 3.1 and 3.2); δ_H (CD_3CN, at -20°C) 1-isomer, 8.07 (d, J = 8 Hz, H-4), 7.68 (d, J = 8 Hz, H-7), 7.50-7.32 (m, H-5,6 and corresponding signals of other isomer), 7.35 (d, J = 9 Hz, MeO-$CC_2H_2C_2\underline{H}_2$, partially overlapping with corresponding signals of other isomer), 6.89 (d, J = 9 Hz, MeO-$CC_2\underline{H}_2$), 6.71 (s, NCHN), 3.70 (m, OCH_2), 3.57 (s, OMe), 2.51 (br s, CH_2N); 2-isomer, 7.93 (AA' m, J = 3 Hz), 7.50-7.32 (BB' m, H-5,6 overlapping with corresponding signals of other isomer and with phenyl protons), 6.79 (s, NCHN), 3.77 (s, OMe), 3.70 (m, OCH_2), 2.51 (br s, CH_2N).

N-[α-(Benzotriazol-N-yl)-β-methyl)propyl]morpholine (3.13). After evaporation of benzene, the product was obtained as an oil which solidified when treated with diethyl ether in a dry ice acetone bath (11.2 g, 65%), m.p. 101-103°C (Found, C, 64.89; H, 8.20; N, 21.79%. $C_{14}H_{20}N_4O$ requires, C, 64.59; H, 7.74; N, 21.52%); δ_H ($CDCl_3$, +21°C) 1-isomer, 8.08 (dd, J = 8 Hz, J = 1 Hz, H-4), 7.59 (d, J = 8 Hz, H-7), 7.45 (td, J = 8 Hz, J = 1 Hz, H-5 or H-6), 7.37 (m, H-6 or H-5, overlapping with corresponding signals of the 2-isomer), 5.01 (d, J = 10 Hz, NCHN), 3.68 (2m, OCH_2), 3.08 (qd, J = 8 Hz, J = 1 Hz, C<u>H</u>Me_2), 2.60 (m, CH_2N), 1.20 (d, J = 10 Hz, CH_3), 0.63 (d, J = 10 Hz, CH_3); 2-isomer, 7.90 (AA' m, J = 3 Hz, H-4,7), 7.37 (BB' m, H-5,6, overlapping with corresponding signals of 1-isomer), 5.10 (s, NCHN), 3.68 (m, OCH_2), 2.97 (qd, J = 8 Hz, J = 1 Hz, C<u>H</u>Me_2), 2.60 (m, CH_2N), 1.20 (d, J = 10 Hz, CH_3), 0.67 (d, J = 10 Hz, CH_3).

N-[α-(Benzotriazol-N-yl)-β-methyl)propyl]-N,N-dibenzylamine (3.14). The compound was obtained as a white solid after complete evaporation of benzene at room temperature (at 0.2 mm Hg), and trituration with dry diethyl ether. N-[α-(Benzotriazol-N-yl)-β-methyl)propyl]-N,N-dibenzylamine was collected by filtration (78%), m.p. 83-85°C (Found, C, 77.76; H, 7.11%. $C_{24}H_{26}N_4$ requires, C, 77.80; H, 7.07, N, 15.12%); δ_H (toluene-d_8, +20°C) 1-isomer, 8.03 (d, J = 8 Hz, H-4), 7.30 (d, J = 8 Hz, H-7),

7.12 (m, rest of ring protons), 6.90 (t, J = 6.5 Hz, H-5 or H-6), 5.01 (d, J = 10 Hz, NCHN), 4.13 (d, J = 14 Hz, CH_2Ph), 3.07 (d, J = 14 Hz, CH_2Ph), 2.95 (m, $C\underline{H}Me_2$), 1.16 (d, J = 10 Hz, CH_3), 0.32 (d, J = 10 Hz, CH_3); 2-isomer, 7.92 (AA' m, J = 3 Hz, H-4,7), 7.44 (BB' m, J = 3 Hz, H-5,6), 7.22-7.06 (m, Ph ring protons of both isomers), 5.31 (d, J = 10 Hz, NCHN), 4.17 (d, J = 14 Hz, $C\underline{H}_2Ph$), 3.17 (d, J = 14 Hz, $C\underline{H}_2Ph$), 2.95 (m, $C\underline{H}Me_2$), 1.07 (d, J = 10 Hz, CH_3), 0.39 (d, J = 10 Hz, CH_3).

N-[α-(Benzotriazol-N-yl)benzyl]piperidine (**3.15**). The oil obtained after evaporation of benzene did not solidify under a variety of conditions. The oily residue (59%) was characterized by its ^{13}C- (Tables 3.1 and 3.2), and ^{1}H-NMR spectra: δ_H (toluene-d_8, +21°C) 1-isomer, 8.02 (m, H-4), 7.25-7.00 (m, H-5,6 and Ph ring protons), 6.61 (s, NCHN), 2.80-2.25 [m, $N(CH_2)_2$], 1.40 [br s, $N(CH_2)_2(C\underline{H}_2)_2$], 1.20-1.00 [m, $N(CH_2)_4C\underline{H}_2$]; 2-isomer, 7.25-7.00 (m, all Bt and Ph ring protons), 6.86 (s, NCHN), 2.80-2.25 [m, $N(CH_2)_2$-], 1.40 [br s, $N(CH_2)_2(C\underline{H}_2)_2$], 1.20-1.00 [m, $N(CH_2)_4C\underline{H}_2$].

3.4.4 Methylation of 5-Nitrobenzotriazole

5-Nitrobenzotriazole (0.5 g, 0.03 mol) was dissolved in aq. 2N NaOH (25 ml) and water (10 ml) was added to achieve a clear solution. Dimethyl sulfate (10 g, 0.076 mol) was added and a yellow precipitate appeared. The suspension was

stirred at room temperature for 1/2 h and at 0°C for 1 1/2 h, then the solid was filtered, washed with water and air dried. The crude solid contained three products, as indicated by TLC (eluted with hexanes/Et_2O, 1/1, v/v) with R_f values 0.62, 0.37, 0.19. A portion of the crude solid (0.25 g) was placed on a silica gel column and eluted with hexanes/Et_2O (8:2, 7:3, 6:4, 5:5, 2:8, v/v) and finally Et_2O. Total recovery 0.20 g, 80%. The following compounds were collected as column fractions (in order of elution):

2-Methyl-5-nitrobenzotriazole. (R_f = 0.62, 0.094 g, 46%, m.p. 180-4°C, lit. [64T211] m.p. 187°C); δ_H (300 MHz, $CDCl_3$) 8.87 (dd, J_m = 2 Hz, J_p = 0.7 Hz, H-4), 8.24 (dd, J_o = 9 Hz, J_m = 2 Hz, H-6), 7.98 (dd, J_o = 9 Hz, J_p = 0.7 Hz, H-7), 4.61 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 146.6 (C-3a or C-5, small br), 143.0 (C-7a), 120.7 (C-6), 119.1 (C-7), 116.0 (C-4), 44.0 (Me).

3-Methyl-5-nitrobenzotriazole. (R_f = 0.37, 0.048 g, 24%, m.p. 154-157°C, lit. [64T211] m.p. not reported) (Found, C, 45.29; H, 3.48%. $C_7H_6N_4O_2.1/2H_2O$ requires, C, 44.92; H, 3.77; N, 29.94%); δ_H (300 MHz, $CDCl_3$), 8.55 (d, J_m = 2 Hz, H-4), 8.27 (dd, J_o = 9 Hz, J_m = 2 Hz, H-6), 8.18 (d, J_o = 9 Hz, H-7), 4.45 (s, 3 H, CH_3); δ_C (75 MHz, $CDCl_3$) 148.0 (C-3a or C-5), 146.8 (C-5 or C-3a), 132.7 (C-7a), 120.9 (C-5), 118.8 (C-7), 106.5 (C-4), 43.8 (CH_3).

1-Methyl-5-nitrobenzotriazole. (R_f = 0.19, 0.06 g, 30%, m.p. 160-2 °C, lit. [64T211] m.p. 163°C); δ_H (300 MHz, $CDCl_3$) 8.99 (d, J_m = 2 Hz, H-4), 8.42 (dd, J_o = 9 Hz, J_m = 2 H,, H-6), 7.69 (d, J_o = 9 Hz, H-7), 4.41 (3 H, s, Me); δ_C (75 MHz, $CDCl_3$) 144.9 (C-3a or C-5, small br), 136.0 (C-7a), 122.4 (C-5), 117.2 (C-3), 109.0 (C-7), 34.70 (Me).

Table 3.7. ^{1}H-NMR chemical shifts of compounds (3.4-3.15) at a single temperature (above coalescence)

No[a]	Solv.	Temp. (°C)	$-NR_2$	R′	CH	Bt
3.4	$CDBr_3$	110	2.8 (br s, 4 H) 1.7 (br s, 4 H)	-[b]	5.6 (s, 2 H)	8.1-7.7 (br m, 4 H) (br m, 4 H)
3.5	$CDCl_3$	45	1.7 (br s, 4 H) 2.7 (br s, 4 H)	-[b]	5.8 (br s, 2 H)	9.1-7.7 (v. br m, 3 H)
3.6[c]	$CDBr_3$	84	2.8 (br s, 4 H) 1.7 (br s, 4 H)	-[b]	5.7 (s, 2 H)	8.0-7.4 (br m, 3 H)
3.7[d]	$CDBr_3$	110	2.8 (br s, 4 H) 1.7 (br s, 4 H)	-[b]	5.5 (s, 2 H)	7.8-7.3(v. br m, 2 H) 2.4 (br s, Me)
3.8	tol-d_8	70	2.9-2.7 (m, 4 H) 1.4 (s, 4 H)	0.9[e] (m, 7 H)	5.3 (d, 1 H) (J = 10 Hz)	7.8 (br s, 2 H) 7.2-7.1 (m, 2 H)
3.9	$CDBr_3$	110	3.6 (br s, 4 H) 2.7 (br s, 4 H)	-[b]	5.4 (s, 2 H)	8.7 (v. br s, 2 H) 7.4 (s, 2 H)
3.10	$CDBr_3$	90	3.9 (br s, 1 H) 3.7 (br s, 3 H) 3.2 (br s, 1 H) 2.6 (br s, 3 H)	-[g]	6.7 (s, 1 H)	7.9 (br m, 3 H)[f] 7.5-7.3 (m, 6 H)
3.11[h]	$CDBr_3$	110	4.1 (br s, 1 H) 3.8 (br s, 3 H) 3.2 (br s, 1 H) 2.8 (br s, 3 H)	-[g]	6.8 (br s) (1 H)	9.5 (v. br s, 1 H) 8.2-7.2 (m, 7 H)

Table 3.7--continued.

No	Solv.	Temp. (°C)	$-NR_2$	R′	CH	Bt
3.12	CD_3CN	60	3.7 (m, 4 H) 2.5 (br m, 3 H) 2.8 (br s, 1 H)	6.85[g] (d, 2 H) 3.7 (s, 3 H)	6.7 (s, 1 H)	9.9 (s, 1 H) 8.6 (br s, 1 H) 8.0-7.7 (m, 1 H) 7.5-7.3 (br m, 3 H)
3.13	CD_3CN	50	3.6 (m, 4 H) 2.6 (m, 4 H)	3.0 (m, 1 H) 1.2 (m, 6 H)	5.1 (d, 1 H) (J = 10 Hz)	8.2-7.7 (m, 2 H) 7.6-7.3 (m, 2 H)
3.14	$CDBr_3$	90	4.2 (br m, 2 H) 3.3 (br m, 2 H)[g]	3.1 (br m) (1 H) 1.2 (m, 3 H)[g] 0.5 (m, 3 H)	5.30 (br s, 1 H)	7.9 (v. br s, 3 H) 7.3 (br m, 6 H)
3.15	tol-d_8	90	2.29 (br m, 4 H) 1.15 (m, 4 H) 0.94 (m, 2 H)	6.80 (m, 5 H)	6.42 (s, 1 H)	7.5 (v. br s, 4 H)

[a] Many peaks did not become entirely sharp, even at several degrees above coalescence. [b] R′ = H. [c] Some decomposition must have occurred as evidenced by additional aliphatic peaks. [d] In addition, δ 3.4 (br m), 2.0 (br m), probably due to free pyrrolidine. [e] The $C\underline{H}Me_2$ signal is hidden under broad peaks. [f] In addition, δ 10.30 (v. br, 1 H). [g] Phenyl protons come together with benzotriazole protons. [h] The spectrum was recorded in $CDBr_3$, since b.p. (CD_3CN) = 82°C and T_c = 84°C in CD_3CN.

CHAPTER 4

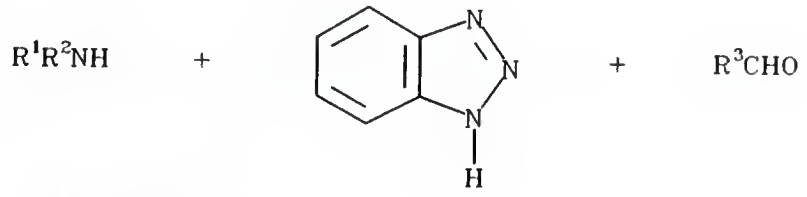
A GENERAL METHOD FOR THE PREPARATION OF STRUCTURALLY DIVERSE TERTIARY AMINES

4.1 Introduction

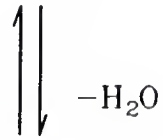
In the preceding chapters, the isomerization of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines was investigated, and the influence of the structure on this process was assessed: all the evidence gathered is in support of the proposed ionic mechanism (Chapter 3, Scheme 3.1). Consequently, the carbon atom located between the benzotriazole and the amine nitrogens (Bt-CH(R)-NR_2) must possess enhanced electrophilicity and therefore is expected to react easily with various nucleophiles. In this and in the following chapters, the reactions of benzotriazole adducts with strong and weak nucleophiles are investigated. The classification is based on the nature of the end-product rather than the type of the reaction.

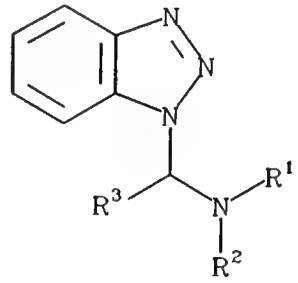
In the present chapter, the knowledge gained so far (Chapter 3) has been combined with previous experience in this [87JCS(P1)805], and other research groups [84TL1635] regarding the reactivity of primary aromatic amine/benzotriazole adducts toward alkylation. Thus, benzotriazole adducts of the type (4.2) are expected to undergo facile alkylation upon reaction with Grignard reagents, thereby

converting secondary amines (**4.1**) into variably substituted tertiary amines (**4.3**). In a similar fashion, replacement of benzotriazole by hydride, by the action of a hydride ion donor, should also be feasible (Scheme 4.1).

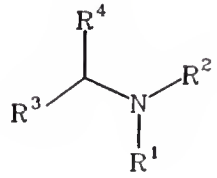


4.1

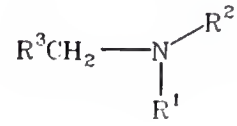




4.2



4.3a – 4.3l



4.3m – 4.3p

Scheme 4.1

Tertiary amines can be prepared by many and varied methods [79MI1]. Alkylation of secondary amines is a useful tool (Equation 4.1); however, in unhindered cases there is danger of over-reaction to yield quaternary salts, and sterically hindered tertiary amines are not easy to prepare in this way, as the reactions are slow and the yields low to moderate [60JA4908], [78S766]. Alkyl branching in R^3X brings with it the probability of competing amine induced β-elimination in substrates having suitably placed hydrogens [79MI1].

$$R^1R^2NH + R^3X \longrightarrow R^1R^2R^3N + HX \qquad \text{(Eq. 4.1)}$$

Reductions of iminium salts (largely confined to formaldehyde derivatives) or tertiary amides [79MI1] (Equations 4.2, 4.3, respectively), require availability of the appropriate precursor and do not allow for versatility in the structural features of the products [79MI1].

$$CH_2O + HNR^1R^2 \longrightarrow CH_2{=}\overset{+}{N}R^1R^2 \xrightarrow{[H^-]} CH_3{-}NR^1R^2 \qquad \text{(Eq. 4.2)}$$

$$R^1CONR^2R^3 \xrightarrow{[H^-]} R^1CH_2NR^2R^3 \qquad \text{(Eq. 4.3)}$$

Reductive carbonylation [83S723] or carboxylation [78S766], [85TL5367] of 2° amines (Equation 4.4), although versatile and high yielding, requires tedious procedures:

$$R^1R^2NH \xrightarrow[2.\ CO_2]{1.\ Bu^nLi} R^1R^2NCO_2^-\ Li^+ \xrightarrow{ClCO_2Me} [\ R^1R^2NCO_2CO_2Me\ ]$$

$$\xrightarrow{\Delta} R^1R^2NCO_2Me \xrightarrow{LiAlH_4} R^1R^2NMe \qquad \text{(Eq. 4.4)}$$

Reductive dealkylation of quaternary ammonium salts [79MI1], often gives good yields but the starting material is usually itself made from a tertiary amine. Deamination of dimethylhydrazinium salts [82SC801] affords N,N-dimethyl-alkyl- or -aryl- amines in high yields, but involves the carcinogenic N,N-dimethylhydrazine (Equation 4.5).

$$RX + Me_2NNH_2 \longrightarrow R(Me)_2N^+NH_2\ X^- \xrightarrow{HNO_2} RNMe_2 \qquad \text{(Eq. 4.5)}$$

The conversion of primary amines with formaldehyde and ethylene glycol into perhydrodioxazepines and subsequent treatment with Grignard reagents [83TL1597] leads to tertiary amines in a more direct way, but is limited to compounds containing two identical alkyl groups (Equation 4.6).

$$RNH_2 + CH_2O + (CH_2OH)_2 \longrightarrow RN(CH_2OCH_2)_2 \xrightarrow{2\ R^1MgX} RN(CH_2R^1)_2$$

(Eq. 4.6)

Methods involving metal catalysts are available [84JOC3359], especially in the patent literature [61MI1], [85JAP60258145] but almost invariably require heating under pressure.

Reaction of organometallic reagents with iminium salts [81JOM275], or chloromethylene iminium salts [85LA2178], provides a direct route to tertiary amines (Equation 4.7), however the required intermediate salts are very hygroscopic [63JOC302], [71AG(E)330].

$$HCONR_2 \xrightarrow{COCl_2} Cl\text{-}CH{=}\overset{+}{N}R_2\ Cl^- \xrightarrow{2\ R^1MgX} R^1_2CH\text{-}NR_2$$

(Eq. 4.7)

In view of the continuous interest in the physiological properties of amines ([59BP814152], [61MI2], [62BEP617762], [63AP728], [79MI1], [87AG(E)320]), new general methods for their preparation are of considerable significance. Within the context of researching the chemistry and properties of benzotriazole derivatives, the possibility of converting the benzotriazole adducts (4.2) into a variety of tertiary amines was investigated.

4.2 Results and Discussion

4.2.1 Preparation of Benzotriazole Adducts

Adducts of type (4.2), as previously shown in Chapters 2 and 3, exist in solution as mixtures of the benzotriazol-1-yl and benzotriazol-2-yl adducts. The preparation of compounds of the type (4.2, R^3 = H) i.e. derived from formaldehyde was reported in Chapter 2. The corresponding adducts (4.2, $R^3 \neq$ H), i.e. derived from higher aldehydes

were prepared by the azeotropic distillation of the water produced from a benzene solution containing benzotriazole, an amine and an aldehyde (Scheme 4.1) in equimolar amounts, as was fully described in Chapter 3. The benzene solutions could be used to react directly with preformed Grignard reagents. Alternatively, the adducts could be isolated, purified and characterized prior to their reaction with the Grignards, although somewhat lower overall yields were then observed, due to unavoidable loses during the isolation step.

An alternative method of preparation of the adducts under milder conditions was also tested. Thus, the three starting materials (Scheme 4.1) were mixed in dry tetrahydrofuran (THF) in the presence of drying agents ($Na_2SO_4/MgSO_4$) and stirred at room temperature for 1-2 days [76JCS(P2)741]; however with this method it was difficult to decide at which point the reversible reaction leading to (**4.2**) (Scheme 4.1) was complete. Grignard reactions using the THF solutions thus obtained, did provide the expected amines (**4.3**) but the yields were low and byproducts, resulting from reaction of the Grignard reagents with the starting aldehyde [eg. $PhCH_2CH(OH)Ph$ from PhCHO and $PhCH_2MgCl$], were detected by GLC/MS. Therefore the azeotropic distillation described above, remained the method of choice.

4.2.2 Preparation of Tertiary Amines

The Grignard reagents, prepared conventionally in ether, reacted very rapidly, and with evolution of heat, with the adducts (**4.2**) yielding tertiary amines (**4.3**) by replacement of benzotriazole (Scheme 4.1, Table 4.1). Amines (**4.3a**)-(**4.3f**) were prepared using THF solutions of the isolated adducts (**4.2a**)-(**4.2d**). Advantageously, adducts (**4.2e**)-(**4.2i**) were not isolated and the benzene solutions from the azeotropic distillation were reacted directly with the Grignard reagents; the overall yields were then very good.

The reactions were generally complete within one hour. The free benzotriazole, obtained after hydrolysis of the reaction mixture, was easily removed by basic extraction (2N NaOH). Byproducts originating from coupling of the Grignard reagents were routinely observed and were removed either by chromatography or by acid extraction of the amine and neutralization of the obtained salt.

Although Grignard reactions are sensitive to steric effects [84MI1] neither retardation of the reaction rate nor side products were observed during the reaction of the dibenzylamine/isobutyraldehyde adduct (**4.2f**) with methylmagnesium iodide, in which the transition state is expected to be sterically crowded.

In a similar fashion, sodium borohydride reduction of the adducts (**4.2a**), (**4.2c**), (**4.2f**) and (**4.2i**) proceeded very smoothly to afford amines (**4.3m**)-(**4.3p**). The reduction

Table 4.1 Preparation of tertiary amines (4.3) $R^4R^3CHNR^1R^2$

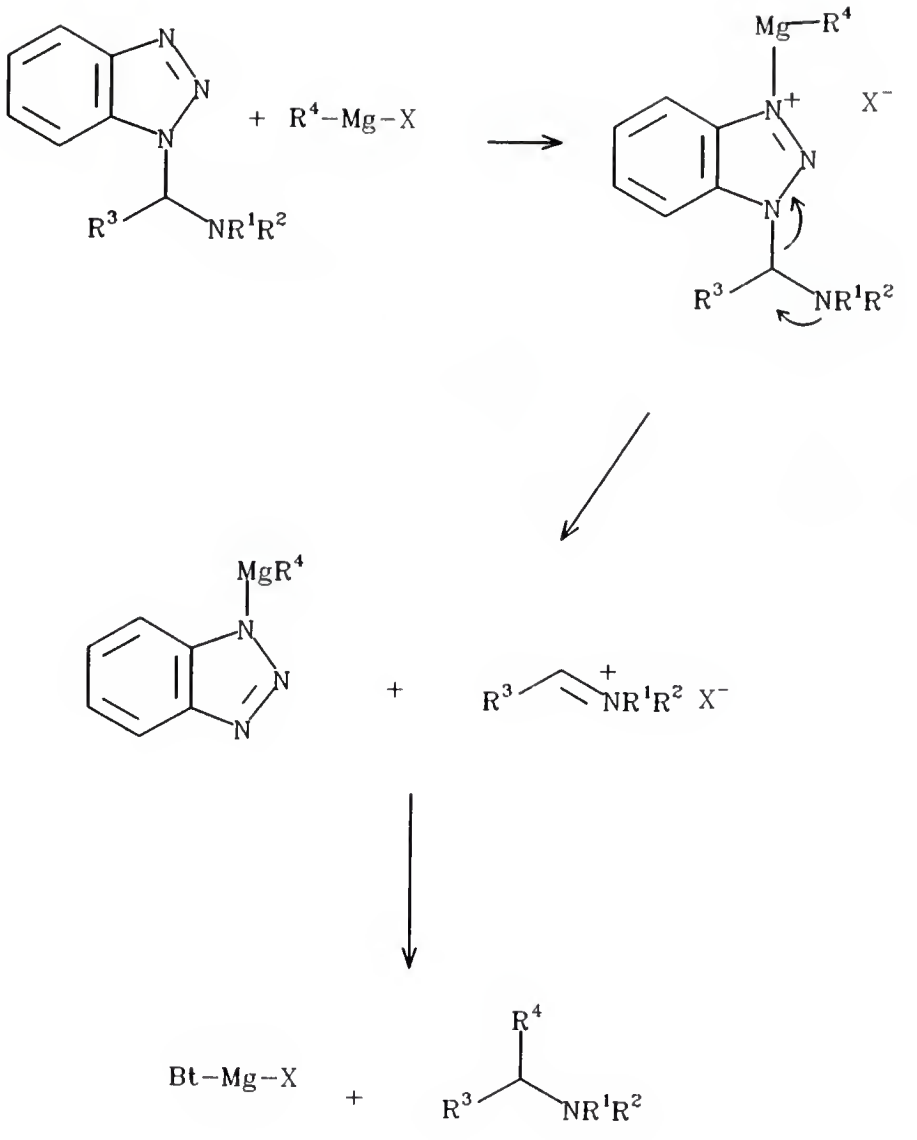
Add. 4.2	R^1	R^2	R^3	Reagent	R^4	Amine 4.3	Yield (%)
a	CH_2Ph	CH_2Ph	H	PhMgBr	Ph	a	83
a	CH_2Ph	CH_2Ph	H	$PhCH_2MgCl$	CH_2Ph	b	88
a	CH_2Ph	CH_2Ph	H	MeMgI	Me	c	80
b	$n\text{-}C_8H_{17}$	$n\text{-}C_8H_{17}$	H	PhMgBr	Ph	d	58
c	CH_3	Ph	H	Bu^nMgBr	Bu^n	e	74
d	Et	Et	H	$PhCH_2MgCl$	CH_2Ph	f	91
e	$-(CH_2)_4-$		Pr^i	$PhCH_2MgCl$	CH_2Ph	g	76[a]
e	$-(CH_2)_4-$		Pr^i	PhMgBr	Ph	h	64[a]
f	CH_2Ph	CH_2Ph	Pr^i	MeMgI	Me	i	78[a]
g	$-(CH_2)_5-$		Ph	Pr^iMgBr	Pr^i	j	59[a]
h	$-(CH_2)_2O(CH_2)_2$		Pr^n	Pr^nMgBr	Pr^n	k	79[a]
i	$-(CH_2)_2O(CH_2)_2$		Ph	Bu^nMgBr	Bu^n	l	82[a]
c	CH_3	Ph	H	$NaBH_4$	H	m	82
a	CH_2Ph	CH_2Ph	H	$NaBH_4$	H	n	75
f	CH_2Ph	CH_2Ph	Pr^i	$NaBH_4$	H	o	83
i	$-(CH_2)_2O(CH_2)_2-$		Ph	$NaBH_4$	H	p	91

[a] This is the overall yield, as calculated from starting benzotriazole; the other numbers in this column, represent yields of the alkylations and reductions, as calculated from the corresponding adduct (4.2).

conditions reported here (simply stirring at room temperature) are milder than those reported for reduction of adducts derived from primary aromatic amines [87JCS(P1)805].

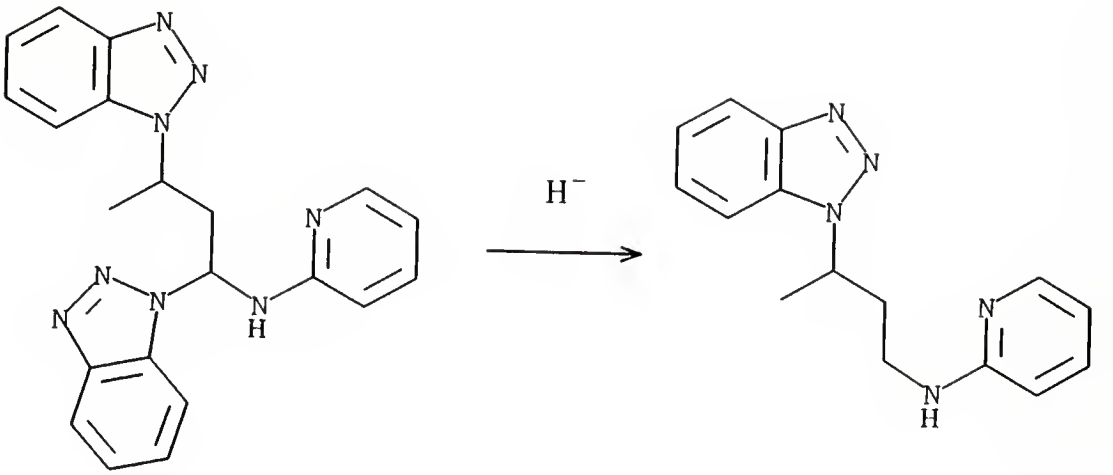
Table 4.1 shows that the products were obtained in generally high yields. The diversity in the structures of the products is also reflected in this Table, in which examples of aliphatic (**4.3k**), or aromatic (**4.3e**) amines, simple (**4.3m**) or sterically crowded (**4.3i**), bearing short (**4.3f**) or long (**4.3d**) aliphatic groups, are collected.

It is not certain whether the Grignard or sodium borohydride reactions proceed <u>via</u> the iminium ion intermediates, invoked in Chapters 2 and 3. The concentration of these reactive intermediates in the solution may be negligible in some cases. On the other hand, the reagents used are reactive nucleophiles, and benzotriazole itself a good leaving group. In addition, no difference in reactivity was displayed among the various adducts toward reactions with the organometallic reagents, although the reactions were fast and slight differences could not have been detected. If indeed an iminium ion is involved, then Grignard addition must be preceded by benzotriazole elimination catalyzed by magnesium acting as a Lewis acid (Scheme 4.2) [84MI1]. The ability of benzotriazole to form complexes with a number of metals is well documented [81ACS(A)739], [83ICA109]. An alternative, but less likely mechanism, is an S_N2 type process, in which the departure of benzotriazole, aided by coordination with the metal, and the nucleophilic attack occur simultaneously.



Scheme 4.2

Independent evidence for the activating role of benzotriazole has been reported previously [87JCS(P1)805] in the reduction of a bis(benzotriazolyl)aminoalkyl adduct, in which only the Bt group α- to the amine was replaced by hydride (Scheme 4.3).



Scheme 4.3

All amines were characterized as their picrate salts and by their ^{1}H- and ^{13}C-NMR spectra (see Experimental section). Chemical shift nonequivalency of the methyl groups of the isopropyl moiety adjacent to the asymmetric carbon atom was observed in the ^{1}H- and ^{13}C-NMR spectra of (**4.3g**), (**4.3h**), and (**4.3i**). Thus, the methyl groups appeared as two doublets in the ^{1}H- and as two distinctly different signals in the ^{13}C-NMR spectra. In spite of their slight complexity, assignments of all spectra were generally possible.

Many of these amines are either novel compounds or found only in the patent literature where they have received considerable interest due to their physiological activity (central nervous system stimulants, antihypertensives, spasmolytics, etc.) [59BP814152], [61GP1093799], [61MI2], [62BEP17762], [63AP728], [85JAP60258145], [87AG(E)320].

4.3 Conclusions

The work described in this Chapter, demonstrates the synthetic utility of benzotriazole adducts in alkylation and reduction reactions, in which facile displacement of the Bt-moiety leads to tertiary amines. The present method has many advantages over other literature methods, including simplicity of procedure, readily available starting materials, possibility for one-pot reaction and good yields. Benzotriazole acts as both an activating and a leaving group and can be recycled at the end, for large scale preparations.

4.4 Experimental

4.4.1 Methods and Reagents

Melting points were determined on a hot stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian XL 200 spectrometer, using TMS (δ = 0.0 ppm) as internal reference. ^{13}C-NMR spectra were recorded either on JEOL FX-100 (25 MHz), or Varian XL 200 (50 MHz) instruments as solutions in deuterochloroform ($CDCl_3$), using the solvent signal at δ = 77.00 ppm as reference.

Exact mass spectra were recorded on a AEI MS 30 mass spectrometer. Combustion analyses were carried out using a Carlo Erba 1106 elemental analyser, under the supervision of Dr. King of this department, or by the Atlantic Microlab.

GLC was carried out on a Hewlett Packard 5890A instrument using a 5 m HP-1 column (conditions: initial temperature = 70°C; initial time = 0 min; rate = 15 deg./min; final temperature = 250°C).

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under nitrogen from sodium/benzophenone immediately before use. Thiophene free, reagent grade benzene (obtained from Fisher Scientific) was used without further drying (0.02 ppm H_2O). Silica gel (230-400 mesh) was purchased from Merck.

4.4.2 Preparation of N-[(α-Benzotriazol-N-yl)alkyl]-N,N-dialkylamines

The preparation of compounds (4.2a)-(4.2c) was based on a general literature procedure [46JA2496] which was described in Chapter 3, with modifications according to the particular compound, as specified below.

N-[(Benzotriazol-N-yl)methyl]-N,N-dibenzylamine (4.2a). Benzotriazole (0.1 mol, 11.9 g), dibenzylamine (0.11 mol, 21.1 ml) and 37% aq. formaldehyde (0.12 mol, 9.7 ml), were mixed in methanol (45 ml). The resulting two-layer system was stirred vigorously at room temperature for 8 h. Diethyl ether was added to homogenize the mixture, and the whole was heated under reflux overnight to complete the reaction. The mixture was then poured on crushed ice, diethyl ether was added and the mixture stirred, resulting

in formation of a white solid. N-[(Benzotriazol-N-yl)methyl]-N,N-dibenzylamine was collected by filtration as white microcrystals (95%), m.p. 120-122°C (from 95% ethanol); lit. [75JCS(P1)1181] m.p. 121-123°C; δ_H ($CDCl_3$, 200 MHz) 8.07-8.02 (d, J = 9 Hz, H-4, 1-isomer), 7.96-.91 (AA' m, J = 8 Hz, H-4, H-7 of 2-isomer), 7.47-7.25 (m, phenyl protons and H-5, H-6 of both isomers), 5.50 (s, NCH_2N, 2-isomer), 5.40 (s, NCH_2N, 1-isomer), 3.79 (s, $NC\underline{H}_2Ph$, 2-isomer), 3.74 (s, $NC\underline{H}_2Ph$, 1-isomer); δ_C ($CDCl_3$, 25 MHz) 145.3 (C-3a, Bt), 137.7 (C-ipso, Ph), 133.7 (C-7a, Bt), 128.7 (C-o, Ph), 128.3 (C-p, Ph), 127.0 (C-m, Ph), 125.3 (C-5 or C-6, Bt), 123.5 (C-6 or C-5, Bt), 119.5 (C-4, Bt), 109.7 (C-7, Bt), 64.0 (NCH_2N), 55.6 ($NC\underline{H}_2Ph$) of the 1-isomer; 143.2 (C-3a, C-7a), 138.1 (C-ipso, Ph), 128.9 (C-o, C-p, Ph), 127.0 (C-m, Ph), 126.0 (C-6, C-5, Bt), 118.2 (C-4, C-7, Bt), 72.0 (NCH_2N), 55.4 ($NC\underline{H}_2Ph$) of the 2-isomer.

N-[(Benzotriazol-N-yl)methyl]-N,N-dioctylamine (**4.2b**). Benzotriazole (0.1 mol, 11.9 g) was dissolved with stirring in methanol (45 ml) and then N,N-dioctylamine (0.11 mol, 26.56 g) was added, followed by 37% aq. formaldehyde (0.12 mol, 9.7 ml). A two layer system resulted which still contained starting materials after 7 h of stirring (TLC on silica gel; eluted with EtOAc:$CHCl_3$, 1:1 v/v). The mixture was made homogeneous with Et_2O and heated under reflux overnight. It was then poured on ice (100 g), extracted with Et_2O (5 x 40 ml), the extracts dried ($MgSO_4$), the

solvent evaporated and the residue heated in vacuo (10 mm Hg, 24 h; 1.5 mm Hg, 1 h), to give an almost colorless thick oil in quantitative yield (38 g). The oil decomposed on attempted distillation (150°C at 0.25 mm Hg). The analytical sample was obtained by drying a small amount of the oil under 10 mm Hg, over P_2O_5 at 78°C for 5 days (Found, C, 74.07; H, 10.85; 14.94%. $C_{23}H_{40}N_4$ requires, C, 74.14; H, 10.82; N, 15.04%); δ_H ($CDCl_3$, 200 MHz) 8.08-8.03 (dd, J = 8, 1 Hz, H-4, Bt, 1-isomer), 7.91-7.86 (AA' m, J = 7 Hz, H-4, H-7, Bt, 2-isomer), 7.62-7.29 (m, H-5, H-6, Bt, both isomers), 5.59 (s, NCH_2N, 2-isomer), 5.48 (s, NCH_2N, 1-isomer), 2.61-2.54 (t, J = 8 Hz, 4 H, NCH_2CH_2, both isomers), 1.56-1.48 (m, 4 H, NCH_2CH_2, both isomers), 1.25 (m, methylene groups, 20 H, both isomers), 0.88 (m, 6 H, CH_3, both isomers); δ_C ($CDCl_3$, 25 MHz), 145.6 (C-3a), 133.6 (C-7a), 126.9 (C-5, or C-6), 123.3 (C-6 or C-5), 119.5 (C-4), 109.7 (C-7), 66.2 (NCH_2N), and octyl group carbons, 51.7 (NCH_2), 31.6, 29.2, 29.1, 27.3, 26.9, 22.9, 13.8 (CH_3) of 1-isomer; 143.9 (C-3a, C-7a), 125.7 (C-5,6), 118.0 (C-4,5), 73.2 (NCH_2N), and octyl group carbons 51.7, 31.6, 29.2, 29.1, 27.3, 26.9, 22.9, 13.8, of the 2-isomer.

N-[(Benzotriazol-N-yl)methyl]-N-methylaniline (**4.2c**). The product was prepared according to literature methods [75JCS(P1)1181] and was collected as white needles (64%), m.p. 72-75°C (from diethyl ether/hexane, 10:1, v/v); lit. [75JCS(P1)1181] m.p. 76-78°C; δ_H ($CDCl_3$, 200 MHz) 7.98-7.93

(d, J = 8 Hz, H-4, 1-isomer), 7.89-7.83 (AA' m, J = 7 Hz, H-4 and H-7, 2-isomer), 7.33-7.25 (m, phenyl groups, both isomers), 7.33-7.25 (m, benzotriazole protons, both isomers), 6.15 (s, NCH_2N, 2-isomer), 6.13 (s, NCH_2N, 1-isomer), 3.30 (s, NCH_3, 2-isomer), 3.01 (s, NCH_3, 1-isomer); δ_C ($CDCl_3$, 25 MHz) 147.7 (C-ipso, Ph), 146.0 (C-3a, Bt), 133.0 (C-7a, Bt), 129.3 (C-o, Ph), 127.3 (C-5 or C-6, Bt), 123.8 (C-6 or C-5, Bt), 119.9 (C-p, Ph), 119.1 (C-7, Bt), 115.1 (C-m, Ph), 110.0 (C-4, Bt), 66.7 (NCH_2N), 37.4 (Me) of 1-isomer, and 144.0 (C-3a and C-7a, Bt), 129.1 (C-o, Ph), 126.7 (C-5, C-6, Bt), 120.0 (C-p, Ph), 118.2 (C-4, C-7, Bt), 113.6 (C-m, Ph), 72.6 (NCH_2N), 38.7 (NCH_3) of 2-isomer.

The preparation and spectroscopic data of N-[(benzotriazol-N-yl)methyl]-N,N-diethylamine (**4.2d**) was described in Chapter 2 (compound **2.6**), and of N-[α-(benzotriazol-N-yl)-β-methylpropyl]pyrrolidine (**4.2e**), N-[α-(benzotriazol-N-yl)-β-methylpropyl]-N,N-dibenzylamine (**4.2f**), N-[α-(benzotriazol-N-yl)benzyl]piperidine (**4.2g**), N-[α-(Benzotriazol-N-yl)benzyl]morpholine (4.2) were described in Chapter 3 [compounds (3.8), (3.14), (3.14), and (3.10), respectively].

N-[α-(Benzotriazol-N-yl)butyl]morpholine (**4.2h**). The compound was prepared using the general method described in Chapter 3, for compounds (3.1, $R^3 \neq H$). After evaporation of solvent benzene under reduced pressure, an oily substance was recovered which was dried under 0.2 mm Hg for several

days. N-[α-(Benzotriazol-N-yl)butyl]morpholine was characterized by its ^{1}H- and ^{13}C-NMR spectra: δ_H (toluene-d_8, 300 MHz) 8.00 (d, J = 8 Hz, H-4, 1 isomer), 7.87-7.84 (AA' m, J = 7 Hz, H-4,7, 2-isomer), 7.15 (d, J = 8 Hz, H-7, 1-isomer), 7.14-7.08 (m, all other ring protons), 5.21 (t, J = 6 Hz, NCHN, 2-isomer), 4.93 (t, J = 6 Hz, NCHN, 1-isomer), 3.44 (m, OCH_2, both isomers), 2.39 (t, J = 4 Hz, CH_2N, 2 H, both isomers), 2.30 (t, J = 4 Hz, CH_2N, 2 H, both isomers, overlapping with signals of the aliphatic chain), 2.10 (m, 2 H, $C\underline{H}_2CH_3$, both isomers), 0.88 (t, J = 6 Hz, 3 H, $CH_2C\underline{H}_3$, both isomers); δ_C ($CDCl_3$, -20°C, 25 MHz) 1-isomer, 145.0 (C-3a), 133.5 (C-7a), 127.1 (C-5 or C-6), 123.7 (C-6 or C-5), 109.7 (C-7), 78.7 (NCH_2N), 66.5 (OCH_2), 47.9 (CH_2N), 32.6 ($NCH\underline{C}H_2CH_2$), 18.6 ($NCHCH_2\underline{C}H_2$), 13.3 (CH_3); 2-isomer, 143.1 (C-3a, C-7a), 126.0 (C-5,6), 117.9 (C-4,7), 85.7 (NCHN), 66.6 (OCH_2), 48.4 (CH_2N), 32.8 ($NCH\underline{C}H_2$), 18.8 ($NCHCH_2\underline{C}H_2$), 13.3 (CH_3).

4.4.3 Preparation of Tertiary Amines by Alkylation: Two-Step Procedure

General method. The Grignard reagent was prepared from magnesium turnings (0.0114 mol) and the alkyl or aryl halide (0.0114 mol) in dry diethyl ether (10 ml). To this solution, the benzotriazole adducts (4.2a)-(4.2d) (0.004 mol) dissolved in dry THF (20 ml) were added dropwise. Immediate frothing and evolution of heat was observed, and reflux was sustained by slow addition. The mixture was heated under reflux for 1 h and then poured on crushed ice

(100 g), and stirred with aq. sat. ammonium chloride (20-50 ml) and/or 1N HCl (10 ml) until all solids dissolved. Extraction with ether (3 x 40 ml), washing with 2N NaOH (until TLC showed no presence of benzotriazole), drying ($MgSO_4$) and removal of the solvent under reduced pressure afforded the crude product which was purified as described for each particular compound. The oily products were characterized as their picrate salts, which were all prepared in and recrystallized from 95% ethanol.

Tribenzylamine (4.3a). Recrystallization of the crude material removed the byproduct biphenyl and afforded tribenzylamine (4.3a) as white flakes (83%), m.p. 91-93°C (from 95% ethanol), lit. m.p. 91-94°C (commercially available from Aldrich Chemical Company); δ_H ($CDCl_3$, 200 MHz) 7.39-7.14 (m, 15 H, aromatic), 5.51 (s, 6 H, Ph-$C\underline{H}_2$); δ_C ($CDCl_3$, 50 MHz) 139.6 (C-ipso), 128.7 (C-o), 128.2 (C-p), 126.8 (C-m), 57.8 (Ph-$\underline{C}H_2$).

N,N-Dibenzyl-N-phenylethylamine (4.3b). The product was obtained as a very clean (as shown by its NMR spectra) pale yellow oil (88%), b.p. 180-185°C (at 0.5 mm Hg); lit. [47JOC760] b.p. 206-211°C (at 3 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.28-7.02 (m, 15 H, aromatic), 3.60 (s, NCH_2Ph, 4 H), 2.87-2.63 (2m, 4 H, N-$C\underline{H}_2C\underline{H}_2Ph$); δ_C ($CDCl_3$, 25 MHz) aromatic (140.5, 139.6, 128.8, 128.6, 125.7, 126.7), 58.1 ($N\underline{C}H_2Ph$), 55.0 ($N\underline{C}H_2CH_2Ph$), 33.4 ($NCH_2\underline{C}H_2Ph$). N,N-Dibenzyl-N-phenylethylamine was characterized as its picrate salt,

m.p. 118-120°C (Found, C, 62.99; H, 4.94; N, 10.36%. $C_{28}H_{26}N_4O_7$ requires, C, 63.39; H, 4.94; N, 10.56).

N-Ethyl-N,N-dibenzylamine (**4.3c**). Distillation of the crude afforded the clean product (80%), b.p. 132-136°C (at 0.5 mm Hg); lit. [78S766] b.p. 101-106°C (at 0.35 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.38-7.17 (m, 10 H, aromatic), 3.54 (s, 4 H, $NC\underline{H}_2Ph$), 2.53-2.43 (q, J = 7 Hz, 2 H, $C\underline{H}_2CH_3$), 1.07-1.00 (t, J = 7 Hz, 3 H, $CH_2C\underline{H}_3$); δ_C ($CDCl_3$, 25 MHz) aromatic (134.0, 128.7, 128.1, 126.7), 57.0 (NCH_2Ph), 47.0 ($\underline{C}H_2CH_3$), 11.8 ($CH_2\underline{C}H_3$). N-Ethyl-N,N-dibenzylamine was converted to its picrate, m.p. 116-118°C; lit. [78S766] m.p. 110-111°C.

N-Benzyl-N,N-dioctylamine (**4.3d**). The product was obtained as a yellow oil, b.p. 110-112°C (at 0.4 mm Hg). A portion of this oil (0.7 g) was purified by column chromatography on silica gel [eluent: hexane, hexane:chloroform (7:3 and then 3:7), chloroform]; 0.435 g of oil were collected (58%) (Found, $M^{+\cdot}$ 331.3253. $C_{23}H_{41}N$ requires, $M^{+\cdot}$ 331.3238); δ_H ($CDCl_3$, 200 MHz) 7.33-7.17 (m, 5 H, aromatic), 3.52 (s, 2 H, $C\underline{H}_2Ph$), 2.42-2.34 (t, J = 7 Hz, 4 H, $NC\underline{H}_2CH_2$), 1.48-1.42 (m, 4 H, $NCH_2C\underline{H}_2$), 1.25 (ap. s, 20 H, methylene groups), 0.90-0.84 (t, J = 6 Hz, 6 H, CH_3); δ_C ($CDCl_3$, 25 MHz) aromatic (140.2, 128.7, 127.9, 126.6), 58.7 (NCH_2Ph), 53.8 ($N\underline{C}H_2CH_2$), methylene groups of N-octyl chain (31.8, 29.5, 29.3, 27.4, 27.0, 22.6), 14.0 (CH_3).

N-Methyl-N-pentylaniline (4.3e). A very clean oil was obtained (73.5%), b.p. 97-98°C (at 0.8 mm Hg); lit. [67JOC2892] b.p. 107-108°C (at 4-5 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.21-6.63 (m, 5 H, aromatic), 3.26-3.19 (t, J = 7 Hz, 2 H, NCH_2), 2.84 (s, 3 H, CH_3), 1.53 (q, J = 7 Hz, 2 H), 1.29 (m, 4 H), 0.89 (t, J = 6 Hz, 3 H, CH_3); δ_C ($CDCl_3$, 25 MHz) 149.3, 128.9, 115.7, 112.9 (aromatic), 52.6 (NCH_2), 38.0 (NCH_3), 29.3 ($NCH_2\underline{C}H_2$), 22.5 ($NCH_2CH_2\underline{C}H_2$), 14.0 ($CH_3$). N-Methyl-N-pentylaniline was converted to its picrate salt, m.p. 94-96°C (Found C, 52.55; H, 5.41; N, 13.65%. $C_{18}H_{22}N_4O_7$ requires, C, 53.20; H, 5.46; N, 13.79%).

N,N-Diethyl-N-phenylethylamine (4.3f). The oily amine [23JCS(1)532] (91%, GLC yield) was converted directly to its picrate, m.p. 90-92°C; lit. [45JCS438] m.p. 93-94°C; NMR spectra of the oil: δ_H ($CDCl_3$, 200 MHz) 7.30-7.12 (m, 5 H, aromatic), 2.69-2.65 (m, 4 H, $PhC\underline{H}_2C\underline{H}_2N$), 2.60-2.50 (q, J = 7 Hz, 4 H, $NC\underline{H}_2CH_3$), 1.06-0.99 (t, J = 7 Hz, 6 H, $NCH_2C\underline{H}_3$); δ_C ($CDCl_3$, 25 MHz) aromatic (140.4, 128.4, 128.1, 126.5), 54.5 ($PhCH_2\underline{C}H_2N$), 46.5 ($Ph\underline{C}H_2CH_2N$), 32.9 ($N\underline{C}H_2CH_3$), 11.3 ($NCH_2\underline{C}H_3$).

4.4.4 Preparation of Tertiary Amines by Alkylation: One-step Procedure

General Method. The Grignard reagents (from 0.04 mol Mg and 0.04 mol halide) in dry diethyl ether (30 ml) were prepared as in section (4.4.3). Adducts (4.2e)-(4.2i) [(0.033 mol), prepared from benzotriazole (0.033 mol), a

secondary amine (0.033 mol) and an aldehyde (0.033 mol) by refluxing in benzene using a Dean-Stark trap, until the calculated amount of water (0.6 ml) had been collected, (cf Chapter 3)] were added dropwise as benzene solutions (without isolation) to the Grignard reagent. The reaction mixture was heated under reflux for 2-4 h and worked up as described in section (4.4.3). For amine (**4.3j**) half amounts of all reagents were used. For (**4.3l**) the adduct (**4.2i**) was isolated, then dissolved (0.004 mol) in benzene (30 ml) and added to the Grignard reagent made from the same amounts as described in section (4.4.3). All amines were characterized as their picrate salts and purified as detailed below for each compound.

N-[(α-Benzyl-β-methyl)propyl]pyrrolidine (**4.3g**). The product was obtained as a very clean oil (76%, yield calculated from benzotriazole), b.p. 105-112°C (at 0.3 mm Hg); lit. [59BP814152] b.p. 88°C (at 0.2 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.30-7.10 (m, 5 H, aromatic), 2.78-2.72 (t, J = 6 Hz, 2 H, $C\underline{H}_2Ph$), 2.56-2.49 [m, 4 H, $N(C\underline{H}_2CH_2)_2$], 2.35-1.55 (m, 1 H, $Me_2C\underline{H}$), 1.72-1.66 [m, 4 H, $N(CH_2C\underline{H}_2)_2$], 0.97-0.92 (2d, J = 7 Hz, 6 H, CH_3); δ_C ($CDCl_3$, 25 MHz) aromatic (143.1, 129.5, 128.5, 125.8), 70.5 (NCH), 51.9 (NCH_2), 35.4 ($\underline{C}H_2Ph$), 31.4 ($\underline{C}HMe_2$), 24.0 [$(NCH_2\underline{C}H_2)_2$], 20.7 ($CH_3$), 18.4 ($CH_3$). N-[(α-Benzyl-β-methyl)propyl]pyrrolidine was derivatized to its picrate salt, m.p. 136-139°C (Found, C, 56.49; H, 6.02; N, 12.41%. $C_{21}H_{26}N4O_7$ requires, C, 56.50; H, 5.87; N, 12.55%).

N-[(α-Phenyl-β-methyl)propyl]pyrrolidine (4.3h). Part of the liquid product (0.51 g) was purified by column (2 cm x 17 cm) chromatography on silica gel packed in chloroform [eluent: chloroform, chloroform/ethyl acetate (6:2 and then 2:6, v/v), ethyl acetate]; a colorless oil was collected (0.38 g, 64%, yield calculated from benzotriazole), b.p. 86-91°C (at 0.25 mm Hg); lit. [62AP728] b.p. 91-98°C (at 0.4 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.27-7.23 (m, 5 H, aromatic), 3.03-3.01 (d, J = 4 Hz, 1 H, NCHN), 2.45-2.41 (m, 2 H, $NC\underline{H}_2CH_2$), 2.28-2.12 (m, 1 H, $C\underline{H}Me_2$), 1.70-1.68 (m, 2 H, $NCH_2C\underline{H}_2$), 0.86-0.74 (2d, J = 7 Hz, 6 H, CH_3); δ_C ($CDCl_3$, 25 MHz) aromatic (139.7, 129.4, 127.2, 126.5), 75.6 (NCH), 51.9 ($N\underline{C}H_2CH_2$), 31.4 ($\underline{C}HMe_2$), 24.0 ($NCH_2\underline{C}H_2$), 20.6 (CH_3), 16.3 (CH_3). N-[(α-Phenyl-β-methyl)propyl]pyrrolidine was converted to its picrate salt, m.p. 129-132°C (Found, C, 55.58; H, 5.50; N, 12.83%. $C_{20}H_{24}N_4O_7$ requires C, 55.55; H, 5.59; N, 12.96%).

N-[(α,β-Dimethyl)propyl]-N,N-dibenzylamine (4.3i). The crude material contained a small amount of dibenzylamine, which was removed by treating the ethereal extracts with conc. HCl. The white precipitate was filtered and the filtrate was washed with aq. 2N NaOH until neutral to pH paper, and then until the organic layer was free of benzotriazole (by TLC). After evaporation of the solvent, and drying, the product was collected as a very clean oil (78%, yield calculated from benzotriazole), b.p. 125-150°C (at 0.2 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.40-7.24 (m, 10 H, aromatic),

3.80-3.73 (d, J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 3.34-3.27 (d, J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 2.30-2.16 (dq, J = 7 Hz, J = 1 Hz, 1 H, $NC\underline{H}Me$), 1.75-1.63 (m, 1 H, $C\underline{H}Me_2$), 1.03-0.96 [2d, J = 8 Hz, 6 H, $CH(C\underline{H}_3)_2$], 0.81-0.77 (d, J = 6.5 Hz, 3 H, $NCHC\underline{H}_3$); δ_C ($CDCl_3$, 25 MHz) aromatic (140.7, 128.8, 128.0, 126.5), 56.0 ($N\underline{C}HMe$), 53.7 ($N\underline{C}H_2Ph$), 31.7 ($\underline{C}HMe_2$), 21.1 [$CH(\underline{C}H_3)CH_3$], 20.6 [$CH(CH_3)\underline{C}H_3$], 9.6 [$NCH(Pr^i)\underline{C}H_3$]. N-[(α,β-Dimethyl)propyl]-N,N-dibenzylamine was converted to its picrate salt, m.p. 124-127°C (Found, C, 60.20; H, 5.84; N, 11.09%. $C_{25}H_{28}N_4O_7$ requires, C, 60.48; H, 5.68; N, 11.28%).

N-[(β-Methyl-α-phenyl)propyl]piperidine (4.3j). After distillation the clean product was an oil (59%), b.p. 107-112°C (at 0.8 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.27-7.08 (m, 5 H, Ph), 2.98-2.93 (d, J = 9 Hz, 1 H, $PhC\underline{H}N$), 2.33-2.19 (m, 4 H, NCH_2), 2.19 (overlapping with the previous signal, 1 H, $C\underline{H}Me_2$), 1.57-1.47 (m, 4 H, $NCH_2C\underline{H}_2$), 1.33-1.02 (m, 2 H, $NCH_2CH_2C\underline{H}_2$), 1.02-0.99 [d, J = 6.5 Hz, 3 H, $CH(C\underline{H}_3)CH_3$], 0.71-0.68 [d, J = 7 Hz, 3 H, $CH(CH_3)C\underline{H}_3$]; δ_C ($CDCl_3$, 25 MHz) aromatic (138.2, 129.0, 128.1, 127.4), 77.0 ($N\underline{C}HPh$), 50.8 ($N\underline{C}H_2$), 28.0 ($\underline{C}HMe_2$), 26.0 ($NCH_2\underline{C}H_2CH_2$), 24.9 ($NCH_2CH_2\underline{C}H_2$), 20.7 [$CH(CH_3)\underline{C}H_3$], 19.6 [$CH(\underline{C}H_3)CH_3$]. N-[(β-Methyl-α-phenyl)propyl]piperidine was converted to its picrate salt, m.p. 157-159°C (Found, C, 56.12; H, 5.90; N, 12.26%. $C_{21}H_{26}N_4O_7$ requires, C, 56.50; H, 5.87; N, 12.55%).

N-Isoheptylmorpholine (4.3k). The product was collected as a very clean oil (79%, yield calculated over

two steps), b.p. 71-74°C (at 0.6 mm Hg); δ_H ($CDCl_3$, 200 MHz) 3.69-3.65 (t, J = 4 Hz, 4 H, CH_2O), 2.52-2.48 (t, J = 4 Hz, 4 H, CH_2N), 2.33-2.27 (t, J = 6.5 Hz, 1 H, NCH), 1.50-1.16 [m, 8 H, $NCH(C\underline{H}_2)_2$], 0.93-0.86 (t, J = 4 Hz, 6 H, CH_3); δ_C ($CDCl_3$, 50 MHz) 67.6 (OCH_2), 63.6 (NCHN), 51.0 (NCH_2), 32.1 ($NCH\underline{C}H_2$), 20.2 ($CHCH_2\underline{C}H_2$), 14.3 (CH_3). N-Isoheptylmorpholine was characterized as its picrate salt, m.p. 115-116.5°C (Found, C, 49.01; H, 6.54; N, 13.02%. $C_{17}H_{26}N_4O_8$ requires, C, 49.27; H, 6.32; N, 13.52%).

N-[α-(Phenyl)butyl]morpholine (4.31). The product was collected as a very clean oil (82%, yield calculated over two steps), b.p. 120-121°C (at 0.6 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.28-7.18 (m, 5 H, aromatic), 3.67-3.61 (m, 4 H, OCH_2), 3.21-3.14 (dd, J = 9 Hz, J = 2 Hz, 1 H, $NC\underline{H}Ph$), 2.41-2.34 (m, 4 H, CH_2N), 1.88-1.83 (m, 1 H, $CH\underline{H}CHPh$), 1.72-1.64 (m, 1 H, $C\underline{H}HCHPh$), 1.26-1.19 (m, 2 H, CH_2), 1.11-1.03 (m, 2 H, CH_2), 0.84-0.76 (t, 3 H, CH_3); δ_C ($CDCl_3$, 25 MHz) aromatic (140.7, 128.4, 127.9, 126.8), 70.5 ($N\underline{C}HPh$), 67.1 (CH_2O), 51.0 (CH_2N), 32.1 ($PhCH\underline{C}H_2$), 20.2 (CH_2), 13.8 (CH_3). N-[α-(Phenyl)butyl]morpholine was characterized as its picrate salt, m.p. 161-162°C (Found, C, 54.20, H, 5.93, N, 11.93%. $C_{21}H_{26}N_4O_8$ requires, C, 54.54; 5.67; 12.11%).

4.4.5 Preparation of Tertiary Amines by Reduction

General method. The adducts (4.2c) (0.01 mol), (4.2b) (0.003 mol), (4.2f) (0.001 mol) and (4.2i) (0.003 mol) in

THF (20 ml, 20 ml, 10 ml and 15 ml, respectively) were each stirred at room temperature with 1 mol equivalent of $NaBH_4$ for 15 h. The reaction was quenched with a small amount of ice (5 g - 15 g), the product extracted with Et_2O, dried ($MgSO_4$) and the solvent was removed under vacuum to give the amines as oils. They were characterized as picrate salts, which were prepared and recrystallized from 95% ethanol.

N,N-Dimethylaniline (**4.3m**). It was obtained as an oil (82%), b.p. 192-193°C (at 760 mm Hg), and characterized by comparison with a commercially available sample [b.p. 193-4°C (at 760 mm Hg)]; δ_H ($CDCl_3$, 200 MHz) 7.23-7.15 (m, 5 H, aromatic), 2.82 (s, 6 H, CH_3); δ_C ($CDCl_3$, 25 MHz) aromatic (150.4, 128.8, 116.5, 112.8), 40.5 (CH_3).

N-Methyl-N,N-dibenzylamine (**4.3n**). After distillation an oily product was collected (75%), b.p. 134-135°C (at 0.7 mm Hg); lit. [76CPB342] b.p. 114-115°C (at 2 mm Hg); δ_H ($CDCl_3$) 7.35-7.15 (m, 10 H, aromatic), 3.51 (s, 4 H, $C\underline{H}_2Ph$), 2.16 (s, 3 H, CH_3); δ_C ($CDCl_3$) aromatic (138.8, 128.9, 128.1, 126.9), 61.6 ($\underline{C}H_2Ph$), 42.0 (CH_3). N-Methyl-N,N-dibenzylamine was characterized as its picrate salt, m.p. 105-108°C; lit. [76CPB342] m.p. 101-103°C.

N-(β-Methylpropyl)-N,N-dibenzylamine (**4.3o**). A clean oily product was collected (83%), b.p. 132°C (at 0.3 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.38-7.18 (m, 10 H, aromatic), 3.50 (s, 4 H, $C\underline{H}_2Ph$), 2.16-2.13 (d, J = 7 Hz, 2 H, NCH_2), 1.91-1.75

(m, 1 H, C<u>H</u>Me_2), 0.87-0.84 (d, J = 7 Hz, 6 H, CH_3); δ_C ($CDCl_3$, 25 MHz) 139.9, 128.8, 128.0, 126.7, 62.2 (N<u>C</u>H_2Ph), 58.8 [N<u>C</u>$H_2(Pr^i)$], 26.1 (<u>C</u>HMe_2), 20.8 (CH_3). N-(β-Methylpropyl)-N,N-dibenzylamine was converted to its picrate salt, m.p. 132-135°C (Found, C, 59.53; H, 5.07; N, 11.93%. $C_{24}H_{26}N_4O_7$ requires, C, 59.74; H, 5.43; N, 11.61%).

<u>N-Benzylmorpholine (4.3p)</u>. A clean oil was obtained (91%), lit. [67JOC272] b.p. 252°C (at 760 mm Hg); δ_H ($CDCl_3$, 200 MHz) 7.30-7.15 (m, 5 H, aromatic), 3.65-3.60 (t, J = 5 Hz, 4 H, CH_2O), 3.39 (s, 2 H, C<u>H</u>$_2$Ph), 2.38-2.33 (t, J = 5 Hz, 4 H, CH_2N); δ_C ($CDCl_3$, 50 MHz) aromatic (137.3, 128.7, 127.8, 126.7), 66.4 (CH_2O), 62.9 (<u>C</u>H_2Ph), 53.1 (CH_2N). N-Benzylmorpholine was converted to its picrate salt, m.p. 186-189°C; lit. [67JOC272] m.p. 188-190°C.

CHAPTER 5

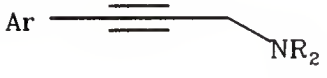
A NEW GENERAL SYNTHESIS OF TERTIARY PROPARGYLAMINES

5.1 Introduction

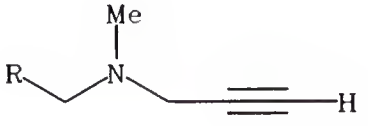
Alkylations of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines *via* Grignard reactions were described in the previous chapter. Given the ease by which these reactions took place, alkylations with other organometallic reagents should also occur readily. Organolithium reagents in general should react, and lithium acetylenides in particular, are expected to replace benzotriazole by an alkynyl group. This part of the research was also expected to test the effect of a different metal and the compatibility of the reaction conditions with the alkynyl group. The resulting products should be tertiary amines bearing a triple bond β- to the nitrogen atom (propargylamines).

Tertiary propargylamines constitute a class of compounds of great pharmacological importance, as reflected by a plethora of reports in the medicinal literature [70MI1]. N,N-Disubstituted-1-aryl-3-aminopropynes (**5.1**) show antiulceration, sedative and antispasmodic effects on smooth muscles, and analgesic-antiinflammatory properties [67BP1055548]. N-(Aminoalkynyl)substituted succinimides and

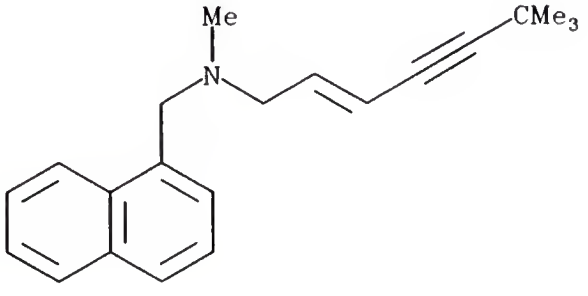
maleimides compose a class of central anticholinergic agents [70JMC651]. N,N-Dialkyl-N-(prop-2-ynyl)amines, commonly called "pargylines" (5.2), have been evaluated *in vitro* and *in vivo*. Thus, N-methyl-N-propargyl-N-benzylamine irreversibly inhibits aldehyde dehydrogenase by oxidative depropargylation to propionaldehyde [79JMC463], while N-(phenylpropyloxy)pargylines showed marked antidepressant activity in severely depressed patients [79MI3]. Finally, compounds possessing the 1,3-enyne structure are biologically active analogues of the important antimycotic terbinafine (5.3), which interferes by squalene epoxidase inhibition in the biosynthesis of ergosterol, a constituent in the cell membranes of fungi [87AG(E)320].



5.1



5.2

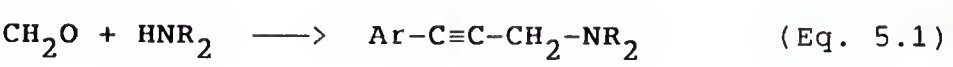


5.3

The biological action of these compounds is thought to be due, at least in part, to the corresponding N-oxides, which are thermally unstable and undergo isomerization to O-allenylhydroxylamines [80OMR161], [81OMR285]. Scheme 5.1 illustrates the Meisenheimer-type rearrangement.

Scheme 5.1

A number of methods exists for the preparation of tertiary propargylamines. Mannich reactions of an arylacetylene with formaldehyde and a secondary amine [33CB418], [73S703], sometimes with a catalytic amount of copper(II) acetate and copper(I) chloride or iodide [67BP1055548], [70JMC651], [78JMC253] give good yields, but are limited to compounds in which the triple bond and N-atom are connected by a methylene group (Equation 5.1). The same compounds can be obtained from reactions of propargyl bromide with secondary amines to give 3-unsubstituted propargylamines [80OMR161], [81OMR285], [87JCR(S)184].



(Eq. 5.1)

Aryl iodides couple with copper acetylenides [78JMC253] to afford propargyl alcohols which are then converted to

propargylamines in two additional steps, making the method rather tedious (Equation 5.2).

$$ArI + Cu\text{-}C{\equiv}C\text{-}CH_2OTHP \xrightarrow{Py} Ar\text{-}C{\equiv}C\text{-}CH_2OTHP \xrightarrow{H^+} Ar\text{-}C{\equiv}C\text{-}CH_2OH$$
$$\xrightarrow{PBr_3} Ar\text{-}C{\equiv}C\text{-}CH_2Br \xrightarrow{HNR_2} Ar\text{-}C{\equiv}C\text{-}CH_2NR_2 \qquad \text{(Eq. 5.2)}$$

According to a recent publication [87JOU1198], aminals react with phenylacetylene in the presence of copper(I) halides to give 3-substituted propargylamines. The scope of this reaction is, however, limited to 3-aryl substituents [72TL3607] (Equation 5.3).

$$R_2N\text{-}CH(Ar)\text{-}NR_2 + Ph\text{-}C{\equiv}C\text{-}H \xrightarrow{CuX} Ph\text{-}C{\equiv}C\text{-}CH(Ar)\text{-}NR_2 \qquad \text{(Eq. 5.3)}$$

3-Substituted propargylamines are produced in base catalyzed rearrangements of allylpropynyl cations, however these reactions are not of synthetic interest [80JCS(P1)1463].

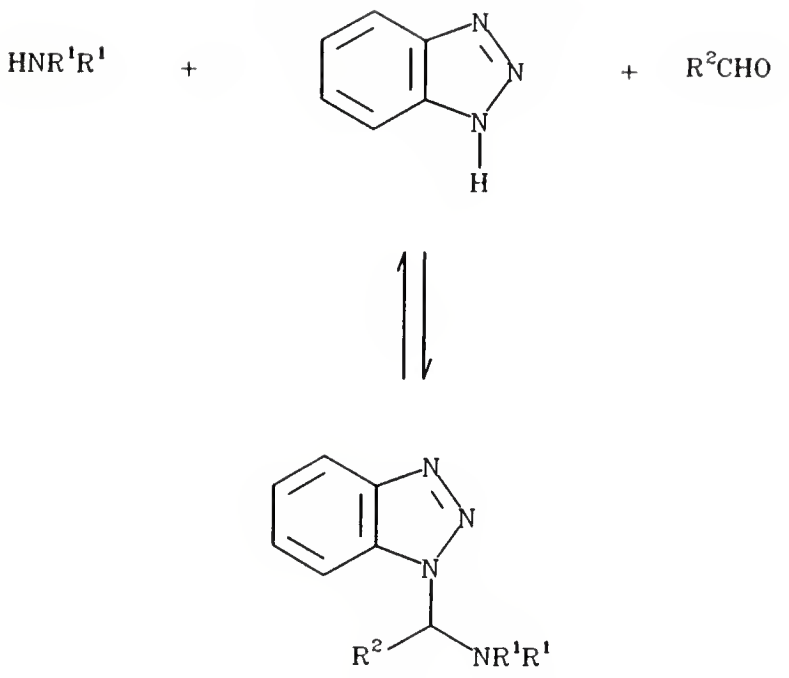
Following new directions in studying the reactivity and versatility of benzotriazole derivatives as synthons (see previous Chapter), the possibility of devising a general methodology for the synthesis of both simple and 3-substituted tertiary propargylamines was investigated.

5.2 Results and Discussion

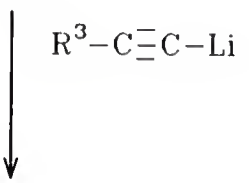
As discussed in Chapter 2, N-[(benzotriazol-N-yl)methyl]-N,N-dialkylamines (5.4, R^2 = H), are readily

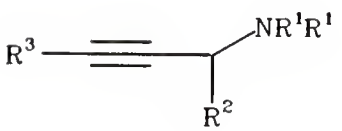
available in almost quantitative yields by reaction of benzotriazole, formaldehyde and the appropriate secondary amine. The corresponding N-[α-(benzotriazolyl)alkyl]-N,N-dialkylamines (5.4, $R^2 \neq H$) can be prepared if another aldehyde is used instead of formaldehyde, as described in Chapters 3 and 4. These latter compounds, need not be isolated: the benzene solutions (see Chapter 4) can be used to react directly at ambient temperature with an equimolar amount of an acetylene lithium salt, prepared in situ by reaction of alkyl- or arylacetylenes with n-butyllithium, to give high yields of the propargylamines (5.5) in an essentially one-pot procedure (Scheme 5.2, Table 5.1).

Satisfactory purity of the products was achieved by simply washing the reaction mixture with 1N sodium hydroxide solution and water, and in some cases passing the resulting oil through a silica gel column. Examples (5.5i)-(5.5n) of Table 5.1 demonstrate that starting from an aldehyde, a secondary amine and an acetylene, the corresponding propargylamines can be obtained in very good overall yields without isolation of the intermediates (5.4). Products (5.5a)-(5.5g) and (5.5i) were characterized as their picrate salts. Except for (5.5b), (5.5c) and (5.5f) all are novel compounds. In all cases, comparison of the ^{1}H- and ^{13}C-NMR spectra to those of structurally similar compounds reported in the literature [80OMR161], [87SA(A)1121], aided the complete characterization of the amines. Specifically, the



5.4





5.5a – 5.5c,h (R^2 = H)

5.5d – 5.5g
5.5i – 5.5n (R^2 = alkyl or aryl)

Scheme 5.2

Table 5.1. Preparation of propargylamines $R^3-C\equiv C-CHR^2-NR^1_2$ (5.5) from benzotriazole adducts $Bt-CH(R^2)-NR^1_2$ (5.4).

Add. 5.4	NR^1_2	R^2	R^3	Amine 5.5	Yield (%)	m.p. (picr.)
a	$N(CH_2Ph)_2$	H	Ph	a	75 [a,b]	172-174
b	$N(CH_2CH_2)_2$	H	Ph	b	73 [a,b]	154-157
c	NMe_2	H	Ph	c	79 [a,b]	115-118
d	$N(CH_2CH_2)_2$	Pr^i	Ph	d	67 [a,b]	116-118
e	$N(CH_2Ph)_2$	Pr^i	Ph	e	95 [b]	130-132
f	$N(CH_2CH_2)_2O$	Ph	Ph	f	33 [a,c]	175-177
e	$N(CH_2Ph)_2$	Pr^i	$n-C_6H_{13}$	g	96 [b]	76-78
g	$N(n-C_8H_{17})_2$	H	$n-C_4H_9$	h	90 [b]	-
h	$N(CH_2CH_2)_2CH_2$	Ph	Ph	i	73 [d]	157-162 [e]
d	$N(CH_2CH_2)_2$	Pr^i	$n-C_6H_{13}$	j	71 [d]	-
i	$N(CH_2CH_2)_2O$	Pr^n	Ph	k	76 [d]	-
i	$N(CH_2CH_2)_2O$	Pr^n	$n-C_6H_{13}$	l	72 [d]	-
j	$N(CH_2CH_2)_2O$	$n-C_7H_{15}$	Ph	m	97 [d]	-
j	$N(CH_2CH_2)_2O$	$n-C_7H_{15}$	$n-C_6H_{13}$	n	81 [d]	-

[a] The yield refers to the product obtained after column chromatography. [b] One-step yield [c] Benzalacetophenone was obtained as the main product in 50% yield. [d] Overall yield based on starting secondary amine. Reactions without isolation of the intermediate N-[α-(benzotriazol-N-yl)-alkyl]-N,N-dialkylamines (5.4) ($R^2 \neq H$). [e] The amine has m.p. 52-55°C (lit. [87JOU1198] m.p. 52-53°C).

acetylenic carbon atoms appeared as two weak resonances between 77.0 and 87.0 ppm in the ^{13}C-NMR spectrum, whereas the characteristic C≡C-$\underline{C}$HR^{2}NR$^1_2$ signals appeared around 50 ppm. In the spectra of compounds bearing two long but not identical aliphatic chains [e.g. (**5.5j**), (**5.5l**)] or in cases where two or more unsymmetrically placed phenyl groups were present, [e.g. (**5.5a**), (**5.5i**)], considerable overlapping of signals was observed, however the majority of resonances could be eventually assigned. The ^{13}C-NMR chemical shifts are collected in Table 6.2.

The ^{1}H-NMR spectra were less descriptive than the ^{13}C-NMR spectra. Several multiplets were observed, especially in compounds with long aliphatic chains. The typical signal of the proton α- to the amino group (-C≡C-C$\underline{H}$R^{2}NR$^1_2$), either as a singlet or as a multiplet, was however always located sufficiently downfield from the bulk of the aliphatic peaks to confirm the correct structure of the compound (see Experimental).

In a few cases [(**5.5h**), (**5.5j**), and (**5.5n**)], attempted vacuum distillation led to partial decomposition of the crude oily amines, as evidenced by additional peaks in the ^{1}H- and ^{13}C-NMR spectrum. It is possible that air oxidation of the initially pure products, resulted in partial formation of the N-oxides, whose facile thermal rearrangement is known to produce O-allenylhydroxylamines (see Scheme 5.1), or even acroleins and imines [80TL667].

Table 5.2. ^{13}C-NMR Chemical shifts (δ) of amines R^3-C≡C-CH(R^2)NR^1_2 (5.5) in $CDCl_3$.

Amine 5.5	R^3	-C≡C-	>CH-	R^2	$-NR^1_2$
a	131.7, 128.2 127.9, 123.3	85.8 84.4	41.9	-	138.8, 128.9 128.2, 127.0 57.6
b[a]	131.5, 128.0 127.7, 123.1	85.1 84.2	43.6	-	52.4, 23.6
c	131.3, 127.8 127.6, 122.9	84.9 84.2	48.1	-	43.8
d	131.6, 128.0 127.6, 123.6	87.6 85.6	62.3	31.9, 20.1 19.4	50.1, 23.5
e	131.8, 128.2	87.3 86.2	59.7	30.8, 21.0 20.0	139.7, 128.9 128.2, 126.9 55.2
f	131.6, 128.0 127.5, 122.8	88.4 84.9	61.8	137.6, 128.4 128.0	49.7, 66.9
g	31.2, 29.1 28.4, 22.5 18.6, 14.9	85.6 77.0	59.1	30.8, 20.8 19.8	139.9, 128.7 128.0, 126.6 54.8
h	31.0, 21.8 18.3, 13.5	84.8 74.6	53.7	-	42.1, 31.8 29.5, 29.2 27.5, 27.4 22.6, 14.0
i	131.7, 128.2 127.3, 123.3	87.8 86.0	62.3	138.6, 128.2 127.9	50.6, 26.1 24.4
j	31.3, 29.1 28.5, 22.5 18.6, 14.0	85.3 77.6	62.2	31.7, 20.1 19.0	23.4, 50.3
k	131.6, 128.1 127.8, 123.1	87.0 86.0	57.7	34.9, 19.7 13.7	49.6, 67.0
l	31.2, 29.0 28.5, 22.5 18.6, 14.0	86.0 77.1	57.3	35.3, 19.8 13.8	49.5, 67.0
m	131.5, 128.0 127.7, 123.1	87.0 85.9	57.9	32.8, 31.6 29.2, 29.0 26.4, 22.5 13.9	49.6, 66.9
n	31.2, 28.9 28.4, 22.4 18.5, 14.0	85.9 77.2	57.6	33.1, 31.7 29.2, 29.1 26.5, 22.5 13.9	49.5, 67.0

[a] Literature data [80OMR161]: δ 131.8, 128.3, 123.6, 85.5, 84.5, 52.7, 43.9, 24.0.

5.3 Conclusions

In this chapter, the utility of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines for synthesis was extended to reactions with lithium acetylenides. A general method of preparation of tertiary propargylamines was developed, which was found to be of wide scope and to have virtually no limitations in the variety of the substituents that can be introduced. The simple, one-pot procedure and the high yields of the products, should make the method very useful for the preparation of propargylamines not readily accessible by previously described methods.

5.4 Experimental

5.4.1 Methods and Reagents

Melting points were measured on a hot-stage apparatus and are uncorrected. ^{1}H (200 MHz) and ^{13}C- (50 MHz) NMR spectra were recorded on a Varian XL 200 (FT mode) spectrometer, using the TMS peak (δ 0.00), and the solvent peak ($CDCl_3$, δ 77.0), respectively as references. Other methods and reagents were described in Chapter 4.

5.4.2 Preparation of N-[α-(Benzotriazol-N-yl)alkyl]-N,N-dialkylamines.

The preparation of the following compounds was carried out as reported previously: N-[(benzotriazol-N-yl)methyl]-

N,N-dimethylamine (5.4c) and N-[(benzotriazol-N-yl)methyl]-pyrrolidine (5.4b), were described in Chapter 2 [compounds (2.3) and (2.4), respectively]. N-[α-(Benzotriazol-N-yl)-β-methylpropyl]pyrrolidine (5.4d), N-[α-(benzotriazol-N-yl)-β-methylpropyl]-N,N-dibenzylamine (5.4e), N-[α-(benzotriazol-N-yl)benzyl]piperidine (5.4h), and N-[α-(benzotriazol-N-yl)benzyl]morpholine (5.4f), were described in Chapter 3 [compounds (3.8), (3.14), (3.15), and (3.10), respectively]. N-[(Benzotriazol-N-yl)methyl]-N,N-dibenzylamine (5.4a), N-(benzotriazol-N-yl)methyl]-N,N-dioctylamine (5.4g) and N-[α-(benzotriazol-N-yl)butyl]morpholine (5.4i) were described in Chapter 4 [compounds (4.2a), (4.2b), and (4.2h), respectively].

N-[α-(Benzotriazol-N-yl)octyl]morpholine (5.4j). The compound was prepared by refluxing equimolar amounts of benzotriazole, morpholine and octanal in benzene, until the theoretical amount of water had been produced (3 days) and the resulting benzene solution was used directly for lithiation (see below). The compound was characterized by its NMR spectra, which showed some line broadening in $CDCl_3$ at room temperature: δ_H ($CDCl_3$, 300 MHz) 8.0 (d, J = 7 Hz, H-4), 7.8-7.2 (br m, all ring protons), 5.43 (m, NCHN, 2-isomer), 5.32 (m, NCHN, 1-isomer), 3.55 (m, OCH_2, both isomers), 2.5 (m, CH_2N), overlapping with 2.35 (m, 2 H, CH_2), 1.2 (m, 10 H), 0.75 (m, 3 H); δ_C ($CDCl_3$, 25 MHz) 1-isomer, 145.3 (C-3a), 133.6 (C-7a), 127.9 (C-5 or C-6),

123.4 (C-6 or C-7), 119.6 (C-4), 109.8 (C-7), 79.3 (NCHN), 66.6 (CH_2O), 48.6 (CH_2NO), aliphatic chain 31.3, 30.9, 30.7, 28.7, 25.3, 22.2, 13.7; 2-isomer, 143.3 (C-3a,7a), 117.9 (C-4,7), 126.9 (C-5,6), 86.1 (NCHN), and aliphatic chain, 31.3, 30.9, 30.7, 28.7, 25.4, 22.2, 13.7.

5.4.3 General Two-Step Procedure for Preparation of Propargylamines.

To a cold (-70°C) solution of the aryl- or alkyl-acetylene (0.005 mol) (see Table 5.1 for the specific alkyl- or aryllithium reagents) in freshly distilled tetrahydrofuran (THF, 20 ml), a solution (2.2 ml) of n-butyllithium (0.0055 mol) in hexane (2.5 M) was added under argon. Stirring at room temperature for 2 h was followed by the addition of the appropriate benzotriazole adduct (5.4) (0.005 mol) dissolved in THF (30 ml). After 1 h the reaction was quenched with a few drops of water, the solvent evaporated under reduced pressure and the residue was dissolved in diethyl ether (150 ml) and washed with 1N sodium hydroxide (50 ml). The aqueous layer was extracted again with diethyl ether (50 ml) and the combined organic solutions were washed with water (100 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure once again. The oil obtained was purified by column chromatography on silica gel eluted with dichloromethane [compounds (5.5a), (5.5d), (5.5i)], dichloromethane/ethyl acetate [compound (5.5b)], and dichloromethane/hexane [compound (5.5f)]. The

yields are reported in Table 5.1. The majority of the products were characterized as their salts with picric acid, which were prepared from 90% ethanol and recrystallized from the same solvent. All elemental analyses data are collected in Table 5.3 (see end of the present Chapter).

N-(3-Phenylprop-2-ynyl)-N,N-dibenzylamine (5.5a). Proton NMR data: δ_H ($CDCl_3$) 7.50-7.35 (m, 6 H, Ph), 7.35-7.15 (m, 9 H), 3.73 (s, 4 H, $PhC\underline{H}_2$), 3.45 (s, 2 H, $C{\equiv}CC\underline{H}N$).

N-(3-Phenylprop-2-ynyl)pyrrolidine (5.5b). Proton NMR data: δ_H ($CDCl_3$) 7.40 (m, 2 H, Ph), 7.26 (m, 3 H, Ph), 3.6 (s, 2 H, $C{\equiv}CC\underline{H}N$), 2.7 (m, 4 H, NCH_2), 1.8 (m, 4 H, $NCH_2C\underline{H}_2$).

N-(3-Phenylprop-2-ynyl)-N,N-dimethylamine (5.5c). Proton NMR data: δ_H ($CDCl_3$) 7.40 (m, 2 H, Ph), 7.25 (m, 3 H, Ph), 3.43 (s, 2 H, $C{\equiv}CC\underline{H}N$), 2.33 (s, 6 H, CH_3).

N-(1-Isopropyl-3-phenylprop-2-ynyl)pyrrolidine (5.5d). Proton NMR data: δ_H ($CDCl_3$) 7.40 (m, 2 H, Ph), 7.20 (m, 3 H, Ph), 3.25 [d, J = 8 Hz, 1 H, $C\underline{H}(Pr^i)$], 2.7 (m, 4 H, NCH_2), 1.9 (m, 1 H, $C\underline{H}Me_2$), 1.76 (m, 4 H, $NCH_2C\underline{H}_2$), 1.10 (d, J = 6 Hz, 3 H, CH_3), 1.05 (d, J = 6 Hz, 3 H, CH_3).

N-(1-Isopropyl-3-phenylprop-2-ynyl)-N,N-dibenzylamine (5.5e). Proton NMR data: δ_H ($CDCl_3$) 7.45 (m, 6 H, Ph), 7.25 (m, 9 H, Ph), 3.90 (d, J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 3.48 (d,

J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 3.15 [d, J = 10 Hz, 1 H, $NC\underline{H}(Pr^i)$], 1.98 (m, 1 H, $C\underline{H}Me_2$), 1.04 (d, J = 6 Hz, 3 H, CH_3), 1.03 (d, J = 6 Hz, 3 H, CH_3).

N-(1,3-Diphenylprop-2-ynyl)morpholine (5.5f). Proton NMR data: δ_H ($CDCl_3$) 7.52 (m, 2 H, Ph), 7.39 (m, 2 H, Ph), 7.18 (m, 6 H, Ph), 4.65 (s, 1 H, CHN), 3.58 (t, J = 4 Hz, 4 H, OCH_2), 2.49 (t, J = 4 Hz, 4 H, CH_2N).

N-(1-Isopropyl-3-hexylprop-2-ynyl)-N,N-dibenzylamine (5.5g). Proton NMR data: δ_H ($CDCl_3$) 7.3 (m, 10 H, Ph), 3.78 (d, J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 3.35 (d, J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 2.85 [d, J = 10 Hz, 1 H, $NC\underline{H}(Pr^i)$], 2.30 (t, J = 6 Hz, 2 H, CH_2), 1.85 (m, 1 H, $C\underline{H}Me_2$), 1.45 (m, 8 H), 0.95 (m, 9 H).

N-(3-Butylprop-2-ynyl)-N,N-dioctylamine (5.5h). Proton NMR data: δ_H ($CDCl_3$) 3.35 (t, J = 2 Hz, 2 H), 2.40 (m, 4 H), 2.2 (m, 2 H), 1.45 (m, 8 H), 1.27 (br m, 20 H), 0.90 (m, 9 H).

5.4.4 General One-Step Procedure for Preparation of Propargylamines

To the lithium acetylene salt (0.005 mol), prepared as indicated above (Section 5.4.3), the appropriate benzotriazole adduct (0.005 mol) in a benzene solution (obtained after heating to reflux equimolar amounts of

benzotriazole, aldehyde and secondary amine in a Dean-Stark apparatus until the theoretical amount of water was collected) was added and the reaction proceeded and worked up as described in Section 5.4.3 above. Analytical samples of the oily products (**5.5k**), (**5.5l**), (**5.5m**) were obtained by column chromatography on silica gel, using as eluents diethyl ether/hexanes. Yields of the overall reactions are reported in Table 5.1. Only (**5.5i**) gave a crystalline picrate, whereas the picrate salts of the other compounds did not solidify. The elemental analyses data are collected in Table 5.3 (see end of this Chapter).

N-(1,3-Diphenylprop-2-ynyl)piperidine (**5.5i**). Proton NMR data: δ_H ($CDCl_3$) 7.64 (m, 2 H, Ph), 7.50 (m, 2 H, Ph), 7.30 (m, 6 H, Ph), 4.78 (s, 1 H, NCHC), 2.55 (br m, 4 H, NCH_2), 1.57 (m, 4 H, $NCH_2C\underline{H}_2$), 1.43 [m, 2 H, $N(CH_2)_2C\underline{H}_2$].

N-(1-Isopropyl-3-hexylprop-2-ynyl)pyrrolidine (**5.5j**). Proton NMR data: δ_H ($CDCl_3$) 3.00 (dt, J = 2 and 7 Hz, 1 H, NCH), 2.60 (m, 4 H, NCH_2), 2.25 (dt, J = 2 and 7 Hz, 1 H), 1.75 (m, 6 H), 1.35 (m, 8 H), 0.95 (m, 9 H, CH_3).

N-(1-Phenyl-3-propylprop-2-ynyl)morpholine (**5.5k**). Proton NMR data: δ_H ($CDCl_3$) 7.41 (m, 2 H, Ph), 7.3 (m, 3 H, Ph), 3.75 (m, 4 H, NCH_2), 3.5 (t, J = 8 Hz, 1 H), 2.71 (m, 2 H, $OCH_2C\underline{H}_2N$), 2.55 (m, 2 H, CH_2), 1.65 (m, 4 H), 0.97 (t, J = Hz, 3 H, CH_3).

N-(3-Hexyl-1-propylprop-2-ynyl)morpholine (5.5l).

Proton NMR data: δ_H ($CDCl_3$) 3.70 (m, 4 H, NCH_2), 3.25 (dt, J = 2 and 7 Hz, 1 H, NCHC), 2.62 (m, 2 H), 2.49 (m, 2 H), 2.21 (dt, J = 2 and 7 Hz, 2 H), 1.40 (m, 12 H), 0.9 (m, 6 H, CH_3).

N-(1-Heptyl-3-phenylprop-2-ynyl)morpholine (5.5m).

Proton NMR data: δ_H ($CDCl_3$) 7.42 (m, 2 H, Ph), 7.27 (m, 3 H, Ph), 3.74 (m, 4 H, OCH_2), 3.46 (t, J = 7 Hz, 1 H, NCHC), 2.70 (m, 4 H, NCH_2), 2.56 (m, 4 H), 1.70 (m, 4 H), 1.5 (m, 4 H), 0.89 (m, 3 H, CH_3).

N-(1-Heptyl-3-hexylprop-2-ynyl)morpholine (5.5n).

Proton NMR data: δ_H ($CDCl_3$) 3.73 (m, 4 H, CH_2O), 3.23 (dt, J = 2 and 7 Hz, 1 H), 2.62 (m, 4 H), 2.50 (m, 2 H), 2.20 (dt, J = 2 and 7 Hz, 2 H), 1.30 (br m, 21 H), 0.90 (m, 6 H, CH_3).

Table 5.3. Characterization of propargylamines (**5.5**)

Amine 5.5[a]	Molecular Formula (FW)	M^+ Found	M^+ Calc.	Found C	Found H	Found N	Required C	Required H	Required N
a	$C_{29}H_{24}N_4O_7$	-	-	64.43	4.45	10.05	64.44	4.48	10.37
b	$C_{19}H_{18}N_4O_7$	-	-	54.86	4.19	13.36	55.07	4.38	13.52
c	$C_{17}H_{16}N_4O_7$	-	-	52.54	4.01	14.45	52.58	4.15	14.43
d	$C_{22}H_{24}N_4O_7$	-	-	57.75	5.30	12.02	57.89	5.30	12.27
e	$C_{32}H_{30}N_4O_7$	-	-	65.60	5.14	9.37	65.97	5.99	9.62
f	$C_{25}H_{22}N_4O_8$	-	-	59.60	4.29	10.81	59.29	4.38	11.06
g	$C_{32}H_{38}N_4O_7$	-	-	64.76	6.88	9.31	65.07	6.48	9.49
h	$C_{23}H_{45}N$	335.3550	335.3552	-	-	-	-	-	-
i	$C_{26}H_{24}N_4O_7$	-	-	61.68	4.74	10.97	61.90	4.80	11.11
j	$C_{16}H_{29}N$	235.2286	235.2299	-	-	-	-	-	-
k	$C_{16}H_{21}NO$	-	-	78.87	8.72	5.71	78.97	8.70	5.76
l	$C_{16}H_{29}NO$	-	-	76.29	11.59	5.53	76.44	11.63	5.57
m	$C_{20}H_{29}NO$	-	-	80.14	9.76	4.68	80.22	9.76	4.68
n	$C_{20}H_{37}NO$	307.2854	307.2874	-	-	-	-	-	-

[a] Compounds (**5.5a**)-(**5.5g**) and (**5.5i**) have been characterized as their picrates.

CHAPTER 6

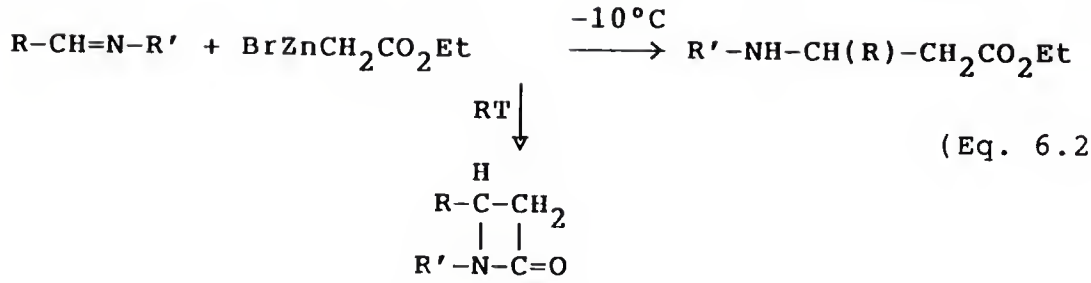
THE PREPARATION OF β-AMINO ESTERS

6.1 Introduction

Powerful nucleophiles, such as organomagnesium and organolithium reagents react easily with N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines (Chapters 4 and 5, respectively). We now show that the above benzotriazole adducts also react with milder nucleophiles. Reformatsky reagents link the ester functionality to the electrophilic substrates (Bt-adducts), yielding β-(N,N-dialkyl)amino esters.

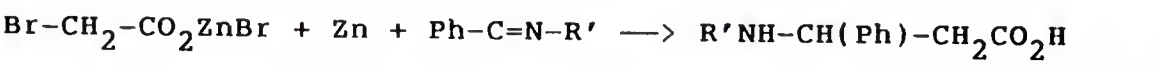
The Reformatsky reaction, is a powerful method of carbon-carbon bond formation under mild conditions [72OCR(A)183], [75OR423]. Classically it involves the synthesis of β-hydroxy esters by reaction of α-bromo esters with carbonyl compounds in the presence of zinc metal. Several examples of modified Reformatsky reactions have been reported, in which substrates other than aldehydes or ketones have been used. Nitriles give, after hydrolysis, β-keto esters [74JOM139] (Equation 6.1), while imines lead to either β-amino esters or β-lactams depending on the reaction conditions [72BSF3841] (Equation 6.2).

$$R\text{-}C{\equiv}N + BrZnCH_2CO_2Et \longrightarrow R\text{-}CO\text{-}CH_2CO_2Et \qquad \text{(Eq. 6.1)}$$



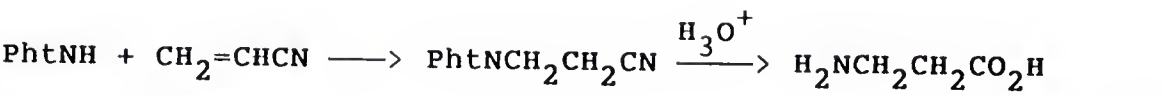
(Eq. 6.2)

In a variation of the latter procedure, salts of α-bromoacids and benzaldimines in the presence of zinc give directly N-monosubstituted β-amino acids [82JOM185] (Equation 6.3), however this method is limited to derivatives of aromatic aldehydes.



(Eq. 6.3)

General methods used in the synthesis of primary β-amino acids, usually <u>via</u> hydrolysis of a suitable precursor, involve the rather lengthy Arndt-Eistert homologation of N-protected α-amino acids [79MI2], and the [2+2] cycloaddition of $ClSO_2NCO$ to olefins under mild but unpleasant conditions (liq. SO_2) to give β-lactams, which are hydrolyzed to β-amino acids [79MI2]. Michael addition of nitrogen nucleophiles to α,β-unsaturated acids, esters or nitriles (Equation 6.4) is an easy route to β-amino acid derivatives, however it can not be used for preparation of α,α-disubstituted products.



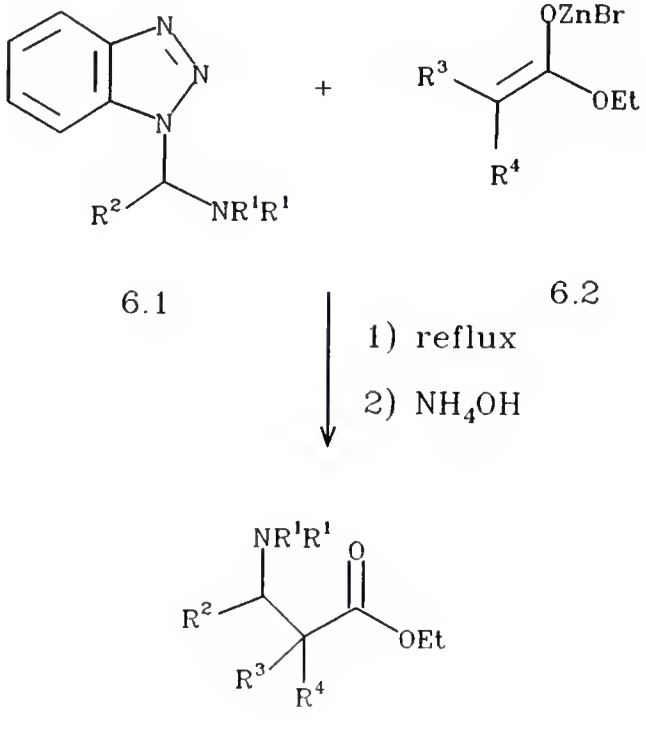
(Pht = phthalyl)

(Eq. 6.4)

Reactions of benzotriazole adducts with Reformatsky reagents are expected to provide an alternative path to both α-mono- and α,α-disubstituted-β-(N,N-dialkyl)amino esters, carrying alkyl or aryl substituents at the β-position.

6.2 Results and Discussion

The reactions of the benzotriazole adducts (**6.1a-f**) with various Reformatsky reagents (**6.2**) (Scheme 6.1) proceeded smoothly, under mild conditions (refluxing in diethyl ether or THF) to give the expected β-amino esters (**6.3**) in good yields (Table 6.1).



6.3

Scheme 6.1

The preparations of compounds (**6.3a**) and (**6.3b**) using conjugate addition of morpholine on commercially available ethyl acrylate [77JHC615], and ethyl cinnamate [62BSF1379], respectively, have been previously reported. However, the rest of the compounds listed in Table 6.1 are novel.

The majority of the prepared β-amino esters represent possibilities in structural diversity not easily accessible by Michael addition or other routes. In the reactions leading to (**6.3d**), (**6.3f**), (**6.3g**), and (**6.3h**), the intermediate benzotriazole adducts (**6.1b**) and (**6.1e**) were not isolated. Instead, direct reaction with the Reformatsky reagents, gave very good yields of the desired products. This demonstrates the "one-pot" possibility of the present method and can be also extended to other examples.

6.2.1 Characterization of the Compounds

The ^{1}H-NMR spectra of some of the products were complicated by the presence of the asymmetric β-carbon atoms (Scheme 6.1). The products of the reactions with ethyl α-bromoisobutyrate the two diastereotopic α-methyl groups gave different signals in the NMR spectra. In the ^{1}H-NMR spectrum of (**6.3h**) even the two methylene protons of the ethoxy group were differentiated, giving two quartets for the $-OCH_2CH_3$ group. Since all products were liquids, characterization was achieved by converting most of them into stable, crystalline picrate salts (Table 6.1), whereas for the remaining products the molecular ion formula was obtained.

Table 6.1 Preparation of β-amino esters (6.3) from benzotriazole adducts (6.1) (see Scheme 6.1).

Add. 6.1	NR^1_2 [a]	R^2	R^3	R^4	Time (h)	Product 6.3	Yield (%)	m.p. (°C) (picrate)
a	Mor	H	H	H	2	a	37[b]	105-108
b	Mor	Pr^i	H	H	1.5	b	85[b]	79-82
c	Mor	Ph	H	H	2	c	84[b]	187-189[e]
b	Mor	Pr^i	Me	H	2	d	82[b,c]	162-164
d	Dib	Ph	Me	Me	18	e	59	oil[f]
b	Mor	Pr^i	Me	Me	2	f	56[c,d]	127-129
e	Pip	Ph	Me	H	21	g	79[c]	oil[f]
e	Pip	Ph	Me	Me	21	h	73[c,d]	200-203
f	Dib	H	Me	Me	3	i	80[d]	197-201

[a] Mor = morpholine; Dib = dibenzylamine; Pip = piperidine. [b] The NMR spectra of the "crude" product (as obtained from the reaction) indicated pure compound. [c] The number represents the overall (two-step) yield as calculated from the secondary amine. [d] Represents the yield of the product after column chromatography. [e] HCl salt (lit. [62BSF1379] m.p. 190°C). [f] The picrate did not crystallize.

6.2.2 Order of Addition

In an initial trial, the reaction was at first carried out using the previously formed Reformatsky reagent

($BrZnCH_2CO_2Et$), to which a solution of the benzotriazole adduct (prepared from N-methylaniline and formaldehyde) was slowly added (Method A). The resulting reaction mixture, however, was not clean, although the desired product was present, as indicated by the NMR spectra of the crude material. Inverse addition (Method B, i. e. adding the Bt-adduct solution to the suspension of Zn, then injecting the bromoester) gave a much cleaner product. Method B was therefore adopted for all the reported reactions. For some examples, especially those requiring long reaction times (see Table 6.1) Method A could also work, but this possibility was not tested.

6.2.3 Reaction Time

Most reactions were complete after a 2-3 hour heating period in either Et_2O or THF/Et_2O solvents. These reaction times proved inadequate for adducts (**6.1d**) and (**6.1e**), whose reactions, after workup, gave either unidentifiable products or mixtures originating from hydrolysis of the starting materials. The results were improved dramatically in both cases when heating was extended over longer periods of time (see Table 6.1), resulting in higher yields and cleaner products. Table 6.1 shows that the morpholine adducts react faster than the other adducts, toward the same nucleophiles. It is possible that the presence of oxygen in morpholine provides additional coordination sites for zinc, and this results to "free" Reformatsky reagent which react faster.

6.2.4 Stereochemistry

In reactions between adducts having an asymmetric carbon atom and ethyl α-bromopropionate, mixtures of diastereomeric products were obtained, as shown by the ^{1}H- and ^{13}C-NMR spectra [see Experimental of compounds (**6.3d**) and (**6.3g**)]. The diastereomeric ratio was nearly 1:1 in the case of (**6.3d**) whereas in the mixture of (**6.3g**) was somewhat greater (5:3). Several solvent systems were tested on TLC but none resulted in separation of the diastereomers.

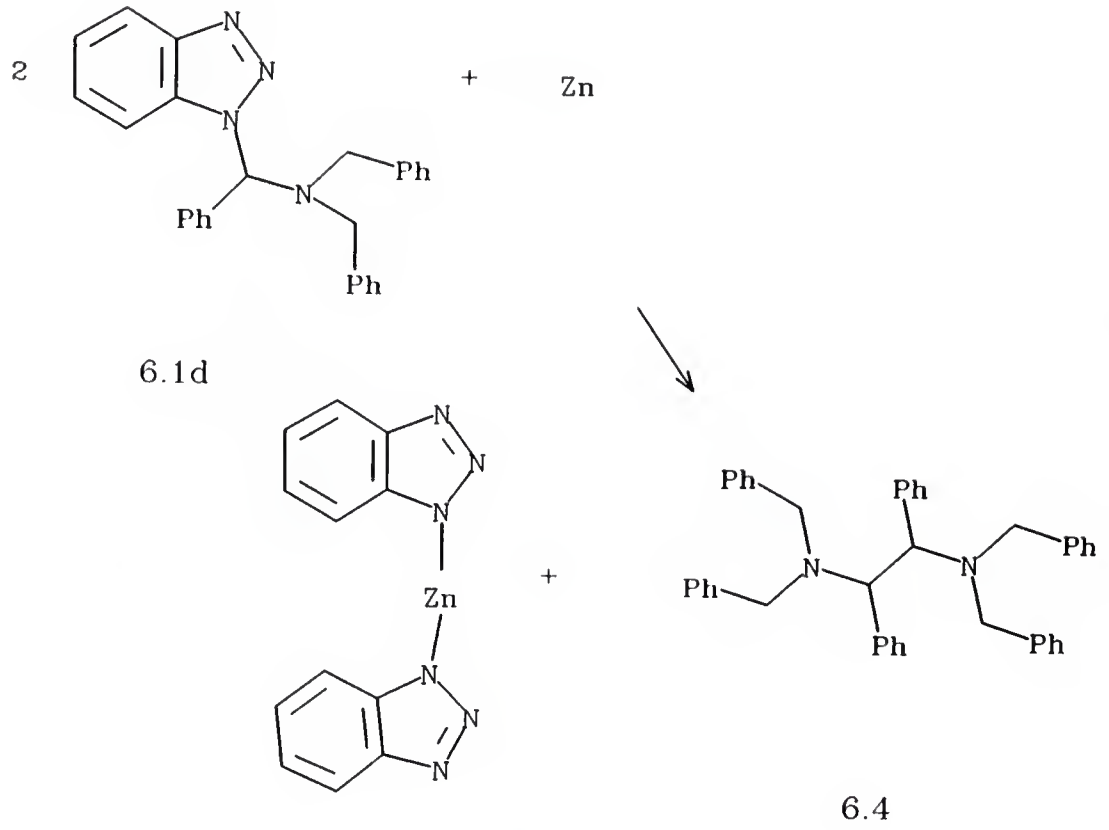
In general, the diastereoselectivity in Reformatsky reactions is moderate [72OCR(A)183], although progress has been reported lately in intramolecular reactions [87JA6556]. In most cases the results can be rationalized with metal chelated structures of minimum steric interactions [75OR423]. Consequently, coordination of benzotriazole with zinc must play a role in the present reactions also: polymeric Bt_4Zn_2 has been well characterized [81ACS(A)739]. The structures of the two transition states leading to products (**6.3d**) and (**6.3g**) should be similar, but the longer reaction time required for (**6.3g**) may be responsible for the higher selectivity observed in this case, since base catalyzed equilibration of the products would favor the thermodynamically more stable isomer. However, general trends and conclusions cannot be drawn, unless more examples are examined.

6.2.5 Side Reactions

In the reaction of (**6.1d**) with ethyl α-bromopropionate and ethyl α-bromoisobutyrate, a side product was consistently isolated as a white solid, which was identified as the dimer (**6.4**) (Scheme 6.2) by ^{1}H-, and ^{13}C-NMR spectra, mass spectra and elemental analysis (see Experimental). This compound was isolated in similar yields (20-22%) regardless of the reaction time (2-18 hours). The same product, in somewhat higher yield (~45%) was isolated from a "blank" experiment in which adduct (**6.1d**) was heated under reflux in a suspension of zinc in THF for three hours.

This product presumably originates from a zinc-mediated coupling of the adduct with removal of two molecules of benzotriazole to form Bt_2Zn or, more accurately, Bt_4Zn_2 [81ACS(A)739] (Scheme 6.2). A radical or radicaloid species, having the tribenzylamine structure and stabilized by resonance, could be responsible for the observed dimerization. In none of the other reactions was the dimer observed, meaning that either it was not formed at all, or was present in undetectable amounts and removed during purification of the products.

Expected α,β-unsaturated ester side products, usually formed in Reformatsky reactions from base-induced elimination of the amine grouping, were not observed. The produced benzotriazole, was removed during the hydrolysis step, which was carried out using cold concentrated ammonium hydroxide.

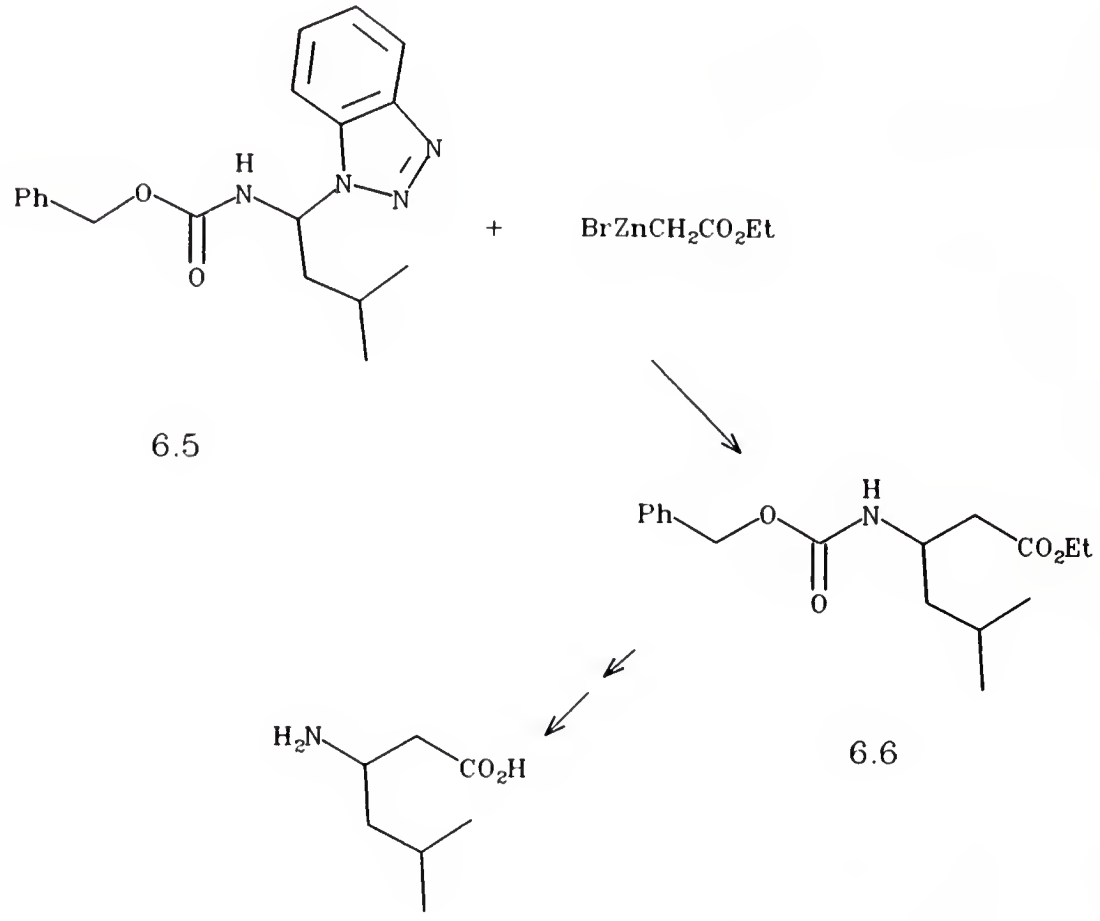


Scheme 6.2

6.2.6 Extension to Different Benzotriazole Adducts

The possibility of extending the Reformatsky reaction to benzotriazole adducts other than those of type (**6.1**), was briefly investigated. Thus, zinc/ethyl bromoacetate reacted easily with adduct (**6.5**) to afford the protected β-amino ester (**6.6**) in about 80% yield (Scheme 6.3). Products of type (**6.6**) are important, since hyrogenolysis of the N-protecting carbobenzyloxy group and hydrolysis of the ester group could eventually give the free β-amino acid (Scheme 6.3).

This example indicates the wide scope of the Reformatsky reactions with benzotriazole adducts and opens new possibilities for successful preparation of a variety of interesting compounds in which the ester group will be introduced (by substitution of benzotriazole) in addition to other existing functionalities.



Scheme 6.3

6.3 Conclusions

A new method for the preparation of the β-(N,N-dialkyl)-amino esters was described in this Chapter, based on the facile replacement of the benzotriazole group in reactions of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines with Reformatsky reagents. The products were obtained in good overall yields. The methods can be also extended to different benzotriazole adducts.

6.4 Experimental

6.4.1 Methods and Reagents

Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone immediately before use. All reactions were carried out under a nitrogen atmosphere. Miscellaneous reagents, purification and characterization methods were described in Chapters 4 and 5. ^{1}H- (300 MHz) and ^{13}C- (75 MHz) NMR spectra were obtained on a Varian VXR 300 spectrometer, unless otherwise stated.

6.4.2 Preparation of Benzotriazole Adducts

The following adducts were prepared as described in Chapter 3: N-[α-(Benzotriazol-N-yl)methyl]morpholine (**6.1a**), N-[α-(benzotriazol-N-yl)-β-methylpropyl]morpholine (**6.1b**), N-[α-(benzotriazol-N-yl)benzyl]morpholine (**6.1c**), N-

[α-(benzotriazol-N-yl)benzyl]piperidine (**6.1e**) [compounds (3.9), (3.13), (3.10), and (3.15), respectively]. N-[α-(Benzotriazol-N-yl)methyl]-N,N-dibenzylamine was described in Chapter 4 [compound (4.2a)]. N-[α-(Benzotriazol-N-yl)-γ-methylbutyl]-N-carbobenzoyloxyamine (**6.6**) was kindly donated by Ms. A. Mayence of our group.

N-[α-(Benzotriazol-N-yl)benzyl]-N,N-dibenzylamine (**6.1d**). Benzotriazole (5.95 g, 0.05 mol), dibenzylamine (9.85 g, 0.05 mol), and benzaldehyde (5.30 g, 0.05 mole) were mixed in benzene and heated under reflux until the calculated amount of water had been collected (0.9 ml, 6 h). The solvent was removed *in vacuo* and the residual oil was triturated with diethyl ether. The resulting precipitate was removed by filtration and dried (76%). N-[α-(Benzotriazol-N-yl)benzyl]-N,N-dibenzylamine was collected as white microcrystals, m.p. 157-160°C (from benzene/Et_2O). (Found, C, 87.45; H, 7.17; N, 5.86%. $C_{35}H_{34}N_2$ requires, C, 87.10; H, 7.10; N, 5.86%); δ_H ($CDCl_3$) 1-isomer, 8.18 (d, J = 8 Hz, H-4), 7.37-7.13 (m, H-5, H-6, and all phenyl protons, both isomers), 6.88 (d, J = 8 Hz, H-7), 6.84 (s, NCHN), 4.25 [d, 2 H, J = 14 Hz, NCH(H)Ph, NC'H'(H')Ph], 3.47 [d, 2 H, J = 14 Hz, NC(H)HPh, NC'(H')H'Ph]; 2-isomer, 8.05 (AA' m, H-4, H-7), 7.73-7.13 (all aromatic protons), 7.00 [s, NCH(Ph)N], 4.25 [d, 2 H, J = 14 Hz, NCH(H)Ph, NC'H'(H')Ph], 3.55 (d, 2 H, J = 14 Hz, CH_2Ph); δ_C ($CDCl_3$): due to the great number of aromatic signals, unequivocal assignment to the 1- or 2-isomer was not possible: 145.2

(C-7a, Bt, 1-isomer), 143.9 (C-3a, C-7a, Bt, 2-isomer), 138.6, 138.4, 136.7, 133.9, 128.7, 128.6, 128.5, 128.4, 128.0, 127.3, 127.2, 127.1, 127.0, 126.9, 126.3, 123.9, 119.8, 118.5, 110.3 (C-7, Bt, 1-isomer), 83.6 [-NCH(Ph)N-, 2-isomer], 75.9 [-NCH(Ph)N-, 1-isomer], 53.7 (NCH_2Ph, 2-isomer), 53.5 (NCH_2Ph, 1-isomer).

6.4.3 General Two-Step Procedure for Preparation of β-Amino Esters

The method reported recently by Picotin and Miginiac [87JOC4796] was adopted. Thus, to a three necked flask, equipped with a reflux condenser and a nitrogen inlet and containing dry zinc powder (0.525 g, 0.008 mol) and anhydrous ether (15 ml), trimethylchlorosilane (0.2 ml, 0.0016 mol) was added. The mixture was stirred for 15 min at room temperature. The benzotriazole adduct (0.005 mol) was added slowly to the suspension of activated zinc as a solution in Et_2O or in THF (20-30 ml). After the mixture was heated to reflux, the heating was stopped, and the pure bromoester (0.005 mol) was added in three portions under nitrogen. The suspension was then heated to mild reflux, and bubbling of nitrogen was stopped. In most cases the grey powder soon turned to a thin white suspension. The reaction was allowed to proceed for the time period indicated in Table 6.1. The mixture was then poured onto conc. ammonium hydroxide (25 ml) containing ice (10 g), and stirred until all solids dissolved. The organic material was extracted with ether (3 x 40 ml), washed with water (2 x

50 ml) and dried ($MgSO_4$). The liquid product was obtained after removal of the solvent under reduced pressure, and purified as indicated for each particular case.

Ethyl 3-morpholinylpropionate (**6.3a**). The compound was a colorless oil (37%); δ_H (60 MHz, $CDCl_3$) 4.2 (q, J = 6 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.7 (m, 4 H, CH_2O, morpholine), 2.5 (m, 8 H, NCH_2, morpholine, and CH_2CH_2CO), 1.3 (t, J = 6 Hz, 3 H, CH_3); δ_C ($CDCl_3$, 25 MHz) 171.6 (C=O), 66.2 (OCH_2, morpholine), 59.7 (OCH_2Me), 53.3 ($N\underline{C}H_2CH_2CO$), 52.8 (NCH_2, morpholine), 31.5 ($NCH_2\underline{C}H_2CO$), 13.6 (CH_3). Ethyl 3-morpholinylpropionate was converted to its picrate salt, m.p. 105-108°C (from 95% EtOH) (Found, C, 43.46; H, 4.83; N, 13.44%. $C_{15}H_{20}N_4O_{10}$ requires, C, 43.27; H, 4.48; N, 13.46%).

Ethyl 4-methyl-3-morpholinylpentanoate (**6.3b**). The product was obtained as a clean liquid (85%); δ_H (200 MHz, $CDCl_3$) 4.13 (q, J = 7 Hz, 2 H, $OC\underline{H}_2Me$), 3.63 (t, J = 5 Hz, 4 H, OCH_2, morpholine), 2.55 [m, 7 H, $C\underline{H}_2NC\underline{H}(Pr^i)C\underline{H}_2CO$], 1.80 (m, 1 H, $C\underline{H}Me_2$), 1.27 (t, J = 7 Hz, 3 H, CH_3), 0.98 [d, J = 8 Hz, 3 H, $CH(CH_3)C\underline{H}_3$], 0.87 [d, J = 8 Hz, 3 H, $CH(C\underline{H}_3)CH_3$]; δ_C (50 MHz, $CDCl_3$) 173.2 (C=O), 67.2 (CH_2O, morpholine), 60.0 ($O\underline{C}H_2Me$), 49.1 (NCH-, overlapping with CH_2N, morpholine), 32.9 ($\underline{C}H_2CO$), 30.0 ($\underline{C}HMe_2$), 20.7 [$CH(CH_3)\underline{C}H_3$], 19.5 [$CH(\underline{C}H_3)CH_3$], 13.9 ($OCH_2\underline{C}H_3$). Ethyl 4-methyl-3-morpholinylpentanoate was characterized as its picrate salt, m.p. 79-82°C (from 95% EtOH) (Found, C, 47.29; H,

5.73; N, 12.43%. $C_{18}H_{26}N_4O_{10}$ requires, C, 47.16; H, 5.72; N, 12.22%).

Ethyl 3-morpholinyl-3-phenylpropionate (6.3c). The product was obtained as a clean oil (84%); δ_H (200 MHz, $CDCl_3$) 7.29 (m, 5 H, Ph), 4.04 (q, J = 7 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.90 (t, J = 8 Hz, 1 H, $NC\underline{H}Ph$), 3.63 (t, J = 5 Hz, 4 H, CH_2O, morpholine), 2.97 [2d, J = 8 Hz, 1 H, $C(H)\underline{H}C{=}O$], 2.62 [2d, J = 8 Hz, 1 H, $C(\underline{H})HC{=}O$], 2.39 (m, 4 H, CH_2N, morpholine), 1.12 (t, J = 7 Hz, 3 H, $OCH_2C\underline{H}_3$); δ_C (25 MHz, $CDCl_3$), 171.2 (C=O), 138.3, 128.8, 128.0, 127.8, 66.8 (OCH_2, morpholine), 66.0 ($O\underline{C}H_2Me$), 59.9 ($N\underline{C}HPh$), 50.1 (NCH_2, morpholine), 38.0 ($\underline{C}H_2CO$), 13.8 ($OCH_2\underline{C}H_3$). Ethyl 3-morpholinyl-3-phenylpropionate was converted into its hydrochloride salt, m.p. 187-189°C (lit. [62BSF1379] m.p. 190°C).

Ethyl 3-dibenzylaminyl-2,2-dimethyl-3-phenylpropionate (6.3e). After workup, the oily residue was triturated with ether and hexanes. The solid that separated [dimeric product (6.4), 22%] was filtered, and the filtrate was concentrated and dried under vacuum (1 cm Hg, 24 h) to give a thick oil (59%); m/z (rel. intensity) 400 (M^+-1, 0.6), 286 (M^+ - Me_2CCO_2Et, 51), 91 (100, C_7H_7); δ_H ($CDCl_3$) 7.35-6.90 (m, 15 H, Ph protons), 3.80 (d, J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 3.75 (s, 1 H, $NC\underline{H}Ph$), 2.95 (d, J = 14 Hz, 2 H, $C\underline{H}_2Ph$), 3.55 (m, 2 H, $OC\underline{H}_2CH_3$), 1.1 (s, 3 H, CH_3), 1.0 (s, 3

H, CH_3), 0.78 (t, J = 7 Hz, 3 H, $OCH_2\underline{C}H_3$); δ_C ($CDCl_3$) 176.5 (C=O), 139.7, 135.8, 130.9, 129.1, 128.7, 128.0, 127.7, 126.8, 69.3 ($N\underline{C}HPh$), 60.3 ($O\underline{C}H_2$), 56.2 ($\underline{C}H_2Ph$), 47.3 ($\underline{C}Me_2$), 25.1 (CH_3), 24.2 (CH_3), 13.7 ($OCH_2\underline{C}H_3$).

Ethyl 3-dibenzylaminyl-2,2-dimethylpropionate (6.3i). After workup and drying, the crude oil (1.67 g) was purified on a column chromatography (silica gel, 21 cm x 2.5 cm) packed in hexane and eluted with hexane/Et_2O (8:2, 7:3, v/v). Ethyl 3-dibenzylaminyl-2,2-dimethylpropionate was collected as a colorless oil (80%); m/z (rel. intensity) 325 (M^+, 3.7), 324 [(M^+-1), 16], 210 (100), 181 (13), 91 (88); δ_H ($CDCl_3$) 7.35-7.20 (m, 10 H, Ph), 4.01 (q, J = 6 Hz, 2 H, OCH_2), 3.53 (s, 4 H, $C\underline{H}_2Ph$), 2.72 (s, 2 H, NCH_2), 1.64 (t, J = 6 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.1 (s, 6 H, $2CH_3$); δ_C ($CDCl_3$) 177.6 (C=O), 139.4, 128.9, 128.0, 126.7, 62.9 ($O\underline{C}H_2CH_3$), 60.2 ($N\underline{C}H_2CMe_2$), 59.2 ($N\underline{C}H_2Ph$), 43.5 ($-\underline{C}Me_2-$), 24.0 (2 CH_3), 14.0 ($OCH_2\underline{C}H_3$). The product was characterized as its picrate salt, m.p. 197-201°C (from 95% EtOH) (Found, C, 55.71; H, 5.45; N, 11.48%. $C_{27}H_{30}N_4O_9.3/2H_2O$ requires, C, 55.76; H, 5.72; N, 9.63%).

6.4.4 General One-step Procedure for Preparation of β-Amino Esters

Adducts (6.1b,e) were prepared by heating a benzene solution of benzotriazole (5.96 g, 0.05 mol), the secondary amine (0.05 mol) and the aldehyde (0.05 mol) in a Dean-Stark

trap until the theoretical amount of water (0.9 ml) had been collected (~15 h). Benzene was removed under reduced pressure and the oily substance (without isolation) was redissolved in Et_2O or Et_2O/THF (1:2, v/v) (70-90 ml). Half volume of the solution (0.025 mol) was added directly to a suspension of activated zinc (2.62 g, 0.04 mol) in Et_2O (25 ml), prepared as described in Section 6.4.3. Addition of the bromoester (0.025 mol) (see Table 6.1) was followed by heating to reflux, for the time specified in Table 6.1. Workup was carried out as in Section 6.4.3.

Ethyl 2,4-dimethyl-3-morpholinylpentanoate (**6.3d**). After workup and drying, ethyl 2,4-dimethyl-3-morpholinyl-pentanoate was obtained as a clean, colorless oil (overall yield 82%), mixture of two diastereomers; δ_H ($CDCl_3$) (signals of both diastereomers given) 4.01 (2q, J = 7 Hz, 2 H, $OC\underline{H}_2CH_3$, both isomers), 3.60 (2d, J = 4 Hz, 1/2 H, one isomer, NCH), 3.45 (q, J = 5 Hz, 4.5 H, OCH_2, morpholine, both isomers, and NCH, second isomer), 2.77-2.45 (3m, 6 H, NCH_2, $MeC\underline{H}C{=}O$, both isomers), 1.92-1.20 (2m, $C\underline{H}Me_2$, both isomers), 1.27 (t, J = 7 Hz, CH_3, OEt, one isomer), 1.26 (t, J = 7 Hz, CH_3, OEt, other isomer), 1.17 [d, J = 6 Hz, $CH(C\underline{H}_3)C{=}O$, one isomer], 1.14 [d, J = 6 Hz, $CH(C\underline{H}_3)CO$, other isomer], 0.96 [d, J = 7 Hz, 3 H, $CH(C\underline{H}_3)CH_3$, one isomer], 0.97 [d, J = 7 Hz, 3 H, $CH(CH_3)C\underline{H}_3$, one isomer], 0.25 [d, J = 7 Hz, $CH(C\underline{H}_3)CH_3$, other isomer]; δ_C ($CDCl_3$) 176.1 (C=O),

175.7 (C=O), 71.5 (NCH, both isomers), 67.7 (OCH_2, morpholine), 67.6 (OCH_2, morpholine), 59.9 ($O\underline{C}H_2CH_3$, both isomers), 51.3 (NCH_2, morpholine), 50.2 (NCH_2, morpholine), 41.6 [$\underline{C}$(Me)CO], 39.9 [$\underline{C}$(Me)CO], 28.8 [CH($\underline{C}$H)$_3$CO], 27.1 [CH($\underline{C}H_3$)CO], 21.1 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 19.9 (CH_3). The oil (most likely only one of the diastereomers) crystallized with picric acid to form the corresponding salt, m.p. 162-164°C (from 95% EtOH) (Found, C, 48.71; H, 6.02; N, 11.90%. $C_{19}H_{28}N_4O_{10}$ requires, C, 48.30; H, 5.97; N, 11.86%).

Ethyl 3-morpholinyl-2,2,4-trimethylpentanoate (**6.3f**). Part of the crude product (1.2 g) was purified by column chromatography on silica gel (50 g) packed in hexane and eluted with hexane and hexane/Et_2O (8:2, 6:4, v/v). After drying (12 h, 1 cm Hg, RT), ethyl 3-morpholinyl-2,2,4-trimethylpentanoate was collected as a yellowish oil (56%); δ_H ($CDCl_3$) 4.09 (q, J = 7 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.59 (m, 4 H, OCH_2, morpholine), 2.98-2.88 (m, 2 H, NCH_2, morpholine), 2.2.78-2.75 (m, 2 H, NCH_2, morpholine), 2.64 (d, J = 10 Hz, 1 H, NCH), 2.00 (m, 1 H, $C\underline{H}Me_2$), 1.25 (t, J = 7 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.27 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.02 (d, J = 10 Hz, 3 H, CH_3), 0.85 (d, J = 10 Hz, 3 H, CH_3); δ_C ($CDCl_3$) 178.2 (C=O), 74.7 (NCH), 67.8 (OCH_2, morpholine), 59.9 ($O\underline{C}H_2CH_3$), 51.9 (NCH_2, morpholine), 48.8 ($\underline{C}$CO), 29.1 (CH_3), 25.4 (CH_3), 23.1 (CH_3), 20.8 (CH_3), 13.9 ($OCH_2\underline{C}H_3$). The product was converted to its picrate salt,

m.p. 127-129°C (from 95% EtOH) (Found, C, 49.48; H, 6.22; N, 11.69%. $C_{20}H_{30}N_4O_{10}$ requires, C, 49.38; H, 6.22; N, 11.52%).

Ethyl 2-methyl-3-phenyl-3-piperidylpropionate (**6.3g**). After drying (1 cm Hg, 1 h, 70°C), ethyl 2-methyl-3-phenyl-3-piperidylpropionate was collected as a very clean pale yellow oil (mixture of two diastereomers, overall yield 79%) (Found, M^+ 275.1924. $C_{17}H_{25}NO_2$ requires, M^+ 275.1882); m/z (rel. intensity) 275 (M^+, 2.4), 91 (32), 117 (12), 174 (100); δ_H ($CDCl_3$) 7.40-7.20 (m, 3 H, Ph), 7.20-7.09 (m, 2 H, Ph), 4.20 (m, $OC\underline{H}HCH_3$, 1.5 H, both isomers), 3.83 (q, J = 7 Hz, 0.5 H, $OC\underline{H}HCH_3$, one isomer), 3.66 (d, J = 12 Hz, 1 H, $NC\underline{H}Ph$, one isomer), 3.64 (d, J = 12 Hz, 1 H, $NC\underline{H}Ph$, other isomer), 3.30-3.10 (2m, 1 H, $C\underline{H}MeCO$, both isomers), 2.55-2.05 (m, 4 H, NCH_2, piperidine, both isomers), 1.6-1.40 (m, 4 H, $NCH_2C\underline{H}_2$, piperidine, both isomers), 1.37 (d, J = 7 Hz, $CHC\underline{H}_3$, one isomer), 1.31 (d, J = 7 Hz, $CHC\underline{H}_3$, other isomer), 1.30-1.20 (m, 2 H, CH_2, piperidine), 0.92 (d, J = 7 Hz, CH_3, OEt, one isomer), 0.87 (d, J = 7 Hz, CH_3, other isomer); δ_C ($CDCl_3$) 175.8 (C=O), 175.4 (C=O), 136.0, 134.5, 129.0, 128.9, 127.7, 127.3, 127.2, 126.9, 73.5 ($N\underline{C}HPh$), 71.5 ($N\underline{C}HPh$), 59.9 ($O\underline{C}H_2CH_3$), 59.8 ($O\underline{C}H_2CH_3$), 50.4 (NCH_2), 50.2 (NCH_2), 41.7 ($NCH_2\underline{C}H_2$), 41.4 ($NCH_2\underline{C}H_2$), 26.4 ($NCH_2CH_2\underline{C}H_2$), 24.5 ($NCH_2CH_2\underline{C}H_2$), 15.5 ($CH_3$), 14.6 ($CH_3$), 14.3 ($CH_3$), 13.7 ($CH_3$). The picrate salt did not crystallize.

Ethyl 2,2-dimethyl-3-phenyl-3-piperidylpropionate (6.3h). Part of the crude oily product (1.8 g) was purified on a silica gel column (22.5 cm x 2.5 cm) packed in petroleum ether (b.p. 40-60°C), and eluted with petroleum ether and petroleum ether/Et_2O (8:2, v/v). Ethyl 2,2-dimethyl-3-phenyl-3-piperidylpropionate was a colorless oil (1.6 g, overall yield 73%); [Found, (M^+-CO_2Et) 216.1733. $C_{15}H_{22}N$ requires, (M^+-CO_2Et) 216.1552]; δ_H ($CDCl_3$) 7.40-7.20 (m, 5 H, Ph), 4.20-4.08 (2q, J = 7 Hz, 2 H, OC<u>H</u><u>H</u>CH_3), 3.83 (s, 1 H, NC<u>H</u>Ph), 2.45-2.20 (2m, 4 H, NCH_2), 1.55-1.40 (m, 4 H, $NCH_2C\underline{H}_2$), 1.40-1.30 (m, 2 H, $NCH_2CH_2C\underline{H}_2$), 1.30 (s, 3 H, CCH_3), 1.22 (t, J = 7 Hz, 3 H, CH_3, OEt), 0.89 (s, 3 H, CCH_3); δ_C ($CDCl_3$) 178.3 (C=O), 139.3, 129.8, 127.4, 126.8, 75.3 (N<u>C</u>HPh), 60.3 (OCH_2), 53.2 (NCH_2), 46.2 (<u>C</u>Me_2), 26.7 ($NCH_2\underline{C}H_2$), 26.5 (CH_3), 24.4 ($NCH_2CH_2\underline{C}H_2$), 19.5 ($CH_3$), 14.0 ($CH_3$, OEt). The product formed a solid with picric acid, m.p. 200-203°C (from 95% EtOH).

6.4.5 Miscellaneous Reactions

Preparation of α,α'-dibenzylaminobibenzyl (6.4). To an ether (20 ml) suspension of zinc (0.525 g, 0.008 mol), activated by addition of trimethylchlorosilane (0.2 ml, stirring at RT for 15 min), N-[α-(benzotriazol-N-yl)benzyl]-N,N-dibenzylamine (6.1d) (1.01 g, 0.0025 mol) was added as a solution in THF (20 ml). The mixture was heated under reflux for 3 h, then poured into iced ammonium

hydroxide (25 ml), extracted with ether (3 x 40 ml), and dried ($MgSO_4$). Following removal of the solvent, the residue was triturated with Et_2O and the resulting solid (1^{st} and 2^{nd} crops, 0.3 g, 42%) was filtered. α,α'-Dibenzylaminobibenzyl was a white crystalline solid, m.p. 248-251°C (Found, C, 86.68; H, 6.95; N, 4.61%. $C_{42}H_{40}N_2$ requires, C, 88.07; H, 7.04; N, 4.89%); m/z (rel. intensity) 286 (M^{+}/2, 63), 181 (12), 91 (100); δ_H ($CDCl_3$) 7.47 (m, 4 H), 7.16-7.07 (m, 20 H, Ph), 6.81 (m, 6 H), 4.42 (s, NC<u>H</u>Ph, 2 H), 3.57 [d, J = 12 Hz, 4 H, C(H)<u>H</u>Ph], 2.88 [d, J = 12 Hz, 4 H, C(<u>H</u>)HPh]; δ_C ($CDCl_3$) 139.1, 130.1, 130.0, 128.8, 127.4, 127.2, 126.7, 126.3, 62.2, 53.3.

<u>Ethyl β-benzyloxycarbonylamino-δ-methylhexanoate (6.6)</u>. The reaction was carried out as described in Section 6.4.2, by heating a solution of N-[α-(benzotriazol-N-yl)-γ-methylbutyl]-N-benzyloxycarbonylamine (**6.5**) (1.69 g, 0.005 mol) and ethyl bromoacetate (0.7 ml, 0.006 mol) in ether (30 ml) for 18 h. After workup, the crude oil was collected (1.22 g, ~80%); m/z (rel. intensity) 308 [(M^{+}+1), 3], 307 (M^{+}, 3), 250 (8), 206 (21), 108 (25), 107 (18), 91 (100), 65 (14); δ_H ($CDCl_3$) 7.18-7.15 (m, 5 H), 5.24 (br d, J = 10 Hz, 1 H, NH), 4.92 (s, 2 H, $PhC\underline{H}_2O$), 3.95 (m, 3 H, NCH, $OC\underline{H}_2CH_3$), 2.33 (m, 2 H, $C\underline{H}_2CO$), 1.50-1.20 (2m, 2 H, $C\underline{H}_2Pr^i$), 1.08-1.03 (t, J = 7 Hz, 4 H, $OCH_2C\underline{H}_3$, $C\underline{H}Me_2$), 0.76 [m, 6 H, $CH(C\underline{H}_3)_2$]; δ_C ($CDCl_3$) 171.3 (EtO<u>C</u>=O), 155.6 (NHC=O), 136.4, 128.2, 128.0, 127.8, 66.2, 64.4, 60.2, 46.2, 43.4, 39.4, 24.7, 22.7, 13.9.

CHAPTER 7

SYMMETRICAL AND UNSYMMETRICAL AMINALS: STUDIES ON THEIR PREPARATION AND EQUILIBRIA

7.1 Introduction

N-[α-(Benzotriazol-N-yl)alkyl]-N,N-dialkylamines react easily with a range of different organometallic reagents. Replacement of benzotriazole gives rise to a variety of α-functionalized N,N-dialkylamines, as shown in Chapters 4, 5 and 6. The presence of the metal ions was considered instrumental in removing benzotriazole by means of a Bt-metal complex. However, according to the results obtained in Chapter 3, some benzotriazole adducts should be highly electrophilic, so that use of organometallic reagents would not be necessary. Thus, reactions of sufficiently reactive adducts with simple nucleophiles such as secondary amines, should take place to afford either symmetrical or unsymmetrical 1,1-diamines.

Aminals (1,1-diamines or gem-diamines) are N,N-acetals formed by the condensation of carbonyl compounds with amines [82MI2]. Aminals are, as expected, sensitive to acids. Their stability depends on their structure and their molecular weight. Decomposition upon heating and hydrolysis under mild conditions constitute a typical behavior of these

compounds. However, compounds derived from secondary amines and aldehydes (Equation 7.1) are generally easier to handle.

$$Ar\text{-}CHO + 2\ RR^1NH \underset{\leftarrow}{\longrightarrow} RR^1N\text{-}\underset{\displaystyle Ar}{\underset{|}{CH}}\text{-}NRR^1 + H_2O \qquad \text{(Eq. 7.1)}$$

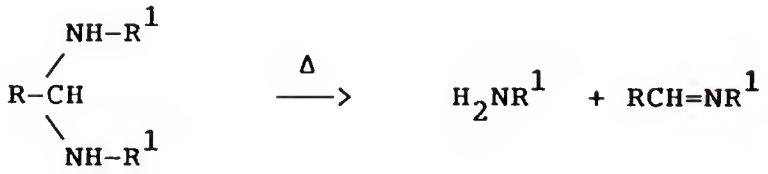
7.1

Aromatic aldehydes react with secondary amines at room temperature or under Dean-Stark conditions to form symmetrical aminals [82MI2] of type (7.1): yields of 50-90% are typical for nucleophilic, unhindered amines (Equation 7.1) [55JA1098], [72MI2]. Older literature [25JA1348] describes the preparation of aminals (7.1) from gem-dihalides, a method useful for the preparation of not easily accessible keto aminals [82MI2]. Compounds (7.1) are stable in alkaline but not acidic media and some are unaffected by heat, so that they may be distilled [79MI1]. However, if the 2-position bears a hydrogen atom, aminals can be easily converted to an enamine and an amine [75BSF908] (Equation 7.2).

$$RR^1N\text{-}\underset{\displaystyle R_2^2C\text{-}H}{\underset{|}{CH}}\text{-}NRR^1 \longrightarrow RR^1NH + R_2^2C{=}CH\text{-}NRR^1 \qquad \text{(Eq. 7.2)}$$

Symmetrical aminals (7.2), derived from primary amines, are often easily formed, especially from aldehydes and aromatic primary amines but they are cleaved to the

corresponding imines and the primary amines upon attempted distillation [65MI1] (Equation 7.3).

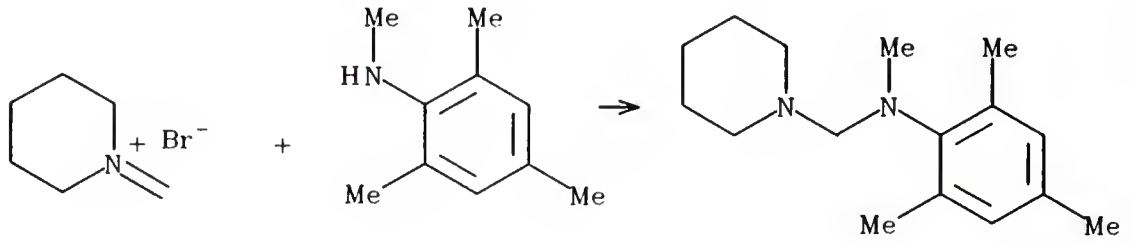


(Eq. 7.3)

7.2

Unsymmetrical aminals are far less known. Zinner reported examples of the type $R_2N-CH_2-NR^1_2$ where R^1 (but not R) was very bulky, prepared by reaction of equimolar amounts of formaldehyde and two different amines in aqueous solution [67CB2515]. Fractional distillation of the resulting mixture afforded the unsymmetrical aminals in yields ranging from 6% to 15%.

Boehme and coworkers reported the formation of unsymmetrical aminals (7.3) by addition of a hindered amine on methylene iminium salts (Scheme 7.1) [67CB2131].

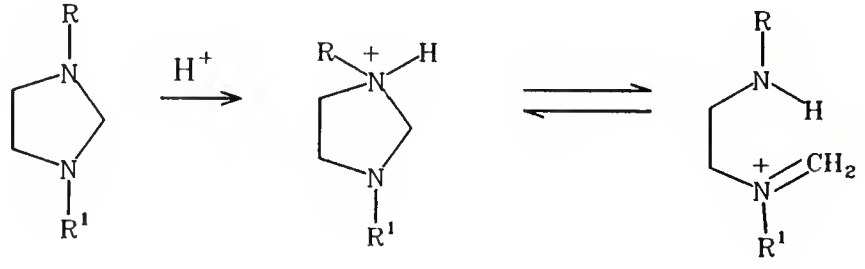


7.3

Scheme 7.1

Reaction of pyrrolidinomethanol with other amines also afforded low yields of unsymmetrical 1,1-methylene diamines. Unsymmetrical aminals derived from aldehydes other than formaldehyde, however, have not been described.

More recently cyclic unsymmetrical aminals of type (7.4) have been prepared [86S657] and studied [87JOC68] by Lambert who found that their cations (7.5) underwent a ring chain tautomerism (7.5) to (7.6) (Scheme 7.2).



7.4 7.5 7.6

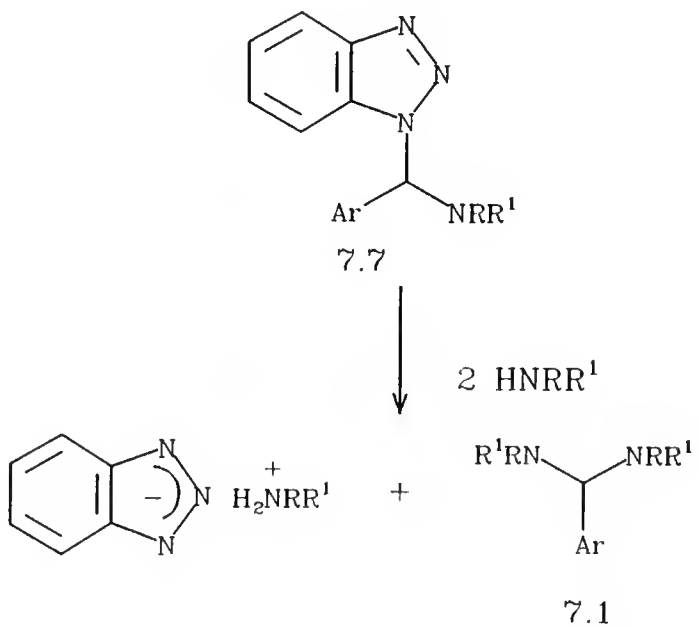
Scheme 7.2

Within the context of exploring the synthetic possibilities of N-[α-(benzotriazol-N-yl)alkyl]-N,N-dialkylamines (see previous Chapters), the reactions of these compounds with secondary amines were investigated. Attempts were particularly focussed on the preparation of unsymmetrical aminals which are not easily accessible by the methods described above.

7.2 Results and Discussion

7.2.1 Preparation of Symmetrical Aminals

Using conventional methods [55JA1098], [72MI2], (Equation 7.1), we carried out a series of reactions to prepare the symmetrical aminals (7.1). The results are collected in Table 7.1 (Method A). The products were characterized by comparing their physical properties with literature values, and by their ^{1}H- and ^{13}C-NMR spectra, which display characteristic signals for the methinic proton NC<u>H</u>(Ar)N at 3.5-4.5 ppm and the corresponding carbon at 78.0-90.0 ppm (in $CDCl_3$). We also found that these compounds are easily prepared by reactions of the benzotriazole adducts (7.7) with secondary amines (Scheme 7.3, Table 7.1, Method B). The adducts (7.7), prepared as described previously, need not be isolated.



7.7

7.1

Scheme 7.3

Table 7.1. Preparation of symmetrical aminals $R^1_2N-CH(Ar)-NR^1_2$ (7.1)

Entry	Aminals 7.1	Ar	NR^1_2	Method A Yield (%)	Method A m.p. (°C)	Method B Adducts 7.7	Method B Yield (%)	Method B m.p. (°C)
1	**a**	Ph	$N(CH_2)_4$	60	36-8	**a**	61	36.5-7.5
2	**b**	Ph	$N(CH_2)_5$	68.5	77-9	**b**	65	75-7
3	**c**	4-MeO-C_6H_4	$N(CH_2)_4O$	90	96-9	**c**	89	98-101
4	**d**	4-MeO-C_6H_4	$N(CH_2)_5$	82	oil	**d**	79	oil
5	**e**	Me_3CH	$N(CH_2)_4O$	no rxn		**e**	no rxn	
6	**f**	Ph	N(Me)Ph	no rxn		**f**	-[a]	
7	**g**	Ph	$N(CH_2Ph)_2$	33	138-41	**g**	-[b]	
8	**h**	Ph	NEt_2	no rxn		**h**	-[a]	
9	**i**	2-furyl	$N(CH_2)_4$	-[c]		-[c]		

[a] The Bt-adduct was successfully prepared but it failed to react with the amine. [b] The Bt-adduct reacted with the amine but the reaction did not go to completion. [c] The desired product was not isolated; tars were obtained instead.

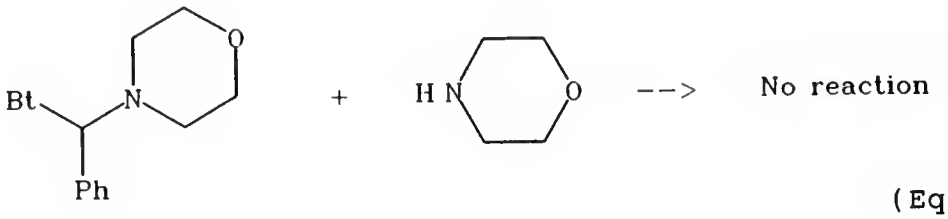
Use of two equivalents of the amine conveniently removed benzotriazole as its amine salt, which precipitated from the solution and therefore the reaction was rapidly driven to completion at room temperature. Alternatively, if one equivalent of the amine was used, benzotriazole could be removed as its sodium salt, by the action of solid or aqueous sodium hydroxide.

The reactivity of adducts (7.7) as related to their structure and the solvent, was discussed in Chapter 3. Here, observations confirming the predicted behavior were made. Thus, adducts (7.7a) and (7.7b), derived from pyrrolidine and piperidine and benzaldehyde, reacted rapidly (3-5 min) with the corresponding amines to afford aminals (7.1a) and (7.1b), respectively (Table 7.1). The high reactivity is a consequence of a low barrier to isomerization of the adducts and higher concentration of the intermediate iminium ions in the solution, in this case captured by the secondary amines (Equation 7.4).

$$Bt\text{-}CH(Ph)\text{-}NR_2 \longrightarrow Bt^- + PhCH{=}\overset{+}{N}R_2 \xrightarrow[-BtH.HNR_2]{+\ 2\ HNR_2} R_2N\text{-}CH(Ph)\text{-}NR_2 \qquad \text{(Eq. 7.4)}$$

As also anticipated, lack of reactivity was displayed by other adducts, under similar, mild conditions. Thus, no reaction took place between morpholine and the corresponding benzaldehyde adduct at room temperature (20 min) (Equation 7.5), whereas the adduct bearing a methoxy group at the

para-position of the phenyl ring reacted very smoothly (Table 7.1, entry 3).



(Eq. 7.5)

Reactions such as that exemplified in Equation 7.4 are of considerable importance in demonstrating the reactivity of some benzotriazole adducts. However, the synthetic value of the benzotriazole method (B) is limited, as shown in Table 7.1, for the following reasons:

(a) The two methods, A and B, are comparable in yield and purity of the resulting symmetrical aminals.

(b) Sterically hindered aminals cannot be prepared by the conventional method A (entries 5, 6 and 8). The corresponding benzotriazole adducts could be prepared, however reaction with 1 equivalent of the amines did not lead to the desired, bulky, symmetrical aminals, under the conditions attempted. The reaction of the benzotriazole adduct with N,N-dibenzylamine in the presence of powdered NaOH did result in the expected product (entry 7), but the reaction was not complete and starting material was present in small amounts even after several days. Purification of the resulting mixture was not successful.

Confirmation of the structure and purity of the aminals, was possible by studying their ^{1}H-, and especially ^{13}C-NMR spectra and by comparing their melting points with literature values whenever possible. Table 7.2 lists the diagnostic ^{13}C-NMR chemical shifts of several symmetrical aminals, prepared as shown in Table 7.1. The presence of the methoxy group does not seem to cause any significant changes, whereas the structure of the amine has a noticeable effect on the chemical shift of the N-CH(Ar)-N carbon atom. Thin layer, column and gas chromatography were proven unreliable, since partial or complete decomposition of the aminal products takes place whenever any of the above techniques was used. Recrystallization could be used as a purification but not as a separation method.

Table 7.2. ^{13}C-NMR chemical shifts of the methinic carbon atom [N-CH(Ar)-N] of symmetrical aminals (7.1) in $CDCl_3$.

7.1	Ar	NR_2^1 [a]	δ (ppm)
a	Ph	Pyr	85.3
b	Ph	Pip	89.8
c	4-MeO-C_6H_4	Mor	88.5
d	4-MeO-C_6H_4	Pip	89.1
g	Ph	Dib	79.6
j	Ph	Mor	88.5

[a] Pyr = pyrrolidine, Pip = piperidine, Mor = morpholine, Dib = dibenzylamine.

In conclusion, the benzotriazole method although does not offer a distinct advantage over the conventional method for the preparation of symmetrical aminals, it demonstrates the high reactivity of some adducts and furnishes evidence for the existence of iminium ion intermediates in the solutions of these compounds.

7.2.2 Preparation of Unsymmetrical Aminals

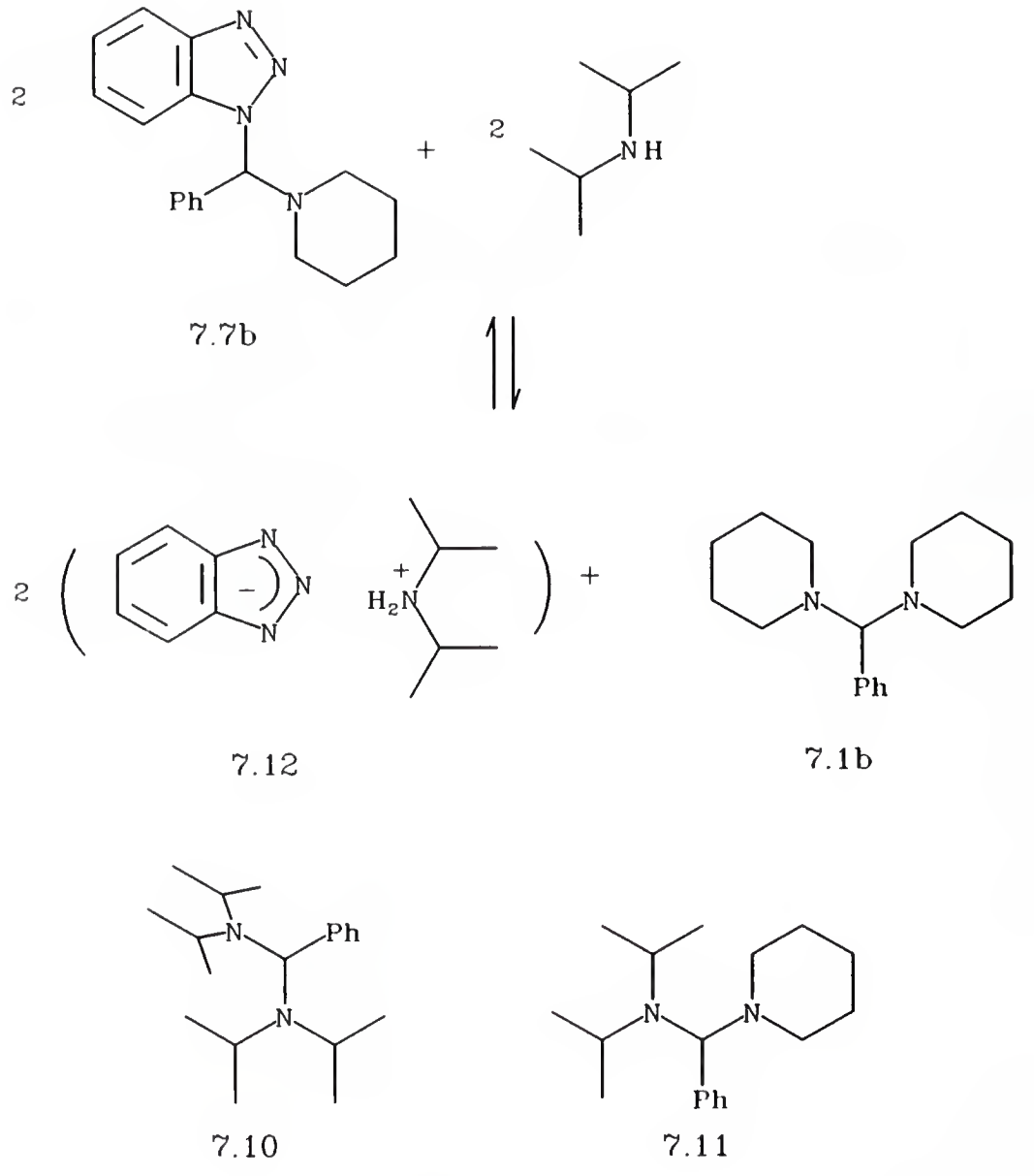
In an attempt to extend the previously described method B to the preparation of unsymmetrical aminals, which are not easily prepared by the conventional methods, we treated the benzotriazole adducts with different amines than those already present in the adducts (Equation 7.6). Attempted GC analysis of the mixture resulted in complete decomposition in the injection port. Analysis of the reaction mixtures was possible only by ^{1}H-, or even better, ^{13}C-NMR spectroscopy, which showed mixtures of the unsymmetrical (7.8) and the two symmetrical aminals, (7.9) and (7.1), regardless of the number of amine equivalents used.

$$3\ \mathrm{Bt{-}CH(Ar){-}NRR^{1}} + 3\ \mathrm{HNR^{2}R^{3}} \xrightarrow{3\ \mathrm{NaOH}} \underset{7.7}{} \qquad \text{(Eq.7.6)}$$

$$3\ \mathrm{BtNa} + \underset{7.8}{\mathrm{R^{1}RN{-}CH(Ar){-}NR^{2}R^{3}}} + \underset{7.9}{\mathrm{R^{3}R^{2}N{-}CH(Ar){-}NR^{2}R^{3}}} + \underset{7.1}{\mathrm{R^{1}RN{-}CH(Ar){-}NRR^{1}}} + 3\ H_{2}O$$

When the reacting amine was very hindered, (e.g diisopropylamine, Scheme 7.4), a fast reaction took place (as indicated by immediate precipitation of a solid), and the unsymmetrical aminal (**7.11**) was initially thought to be present, since a ^{13}C-NMR spectrum of the mixture revealed new carbon signals in addition to those of the benzotriazole adduct. Formation of the symmetrical aminals (**7.1b**) and (**7.10**) (Scheme 7.4) was also considered possible. However, the reaction required a long time and starting material (**7.7b**) was detected, in some cases, even two weeks later and after repeated workups to remove the side benzotriazole salts. This behavior indicated an equilibrium process: the produced benzotriazole amine salt (**7.12**) presumably reacted with the aminal to give a benzotriazole adduct (Scheme 7.4).

This hypothesis was tested by recording the ^{13}C-NMR spectrum of a mixture of diisopropylamine-benzotriazole salt (**7.12**) (prepared from benzotriazole and diisopropylamine in benzene) and aminal (**7.1b**) in $CDCl_3$: a typical 1-substituted benzotriazole pattern consisting of six peaks was observed (see Chapter 2). The spectrum was in all respects identical to that obtained by the forward reaction (Scheme 7.4). The diagnostic N-C<u>H</u>(Ar)-N region suggested that in both forward and reverse reactions, the major component of the mixture was the simple symmetrical aminal (**7.1b**), whereas the unsymmetrical desired product (**7.11**) was very minor (if this assignment is correct) and the sterically crowded aminal (**7.10**) non-existent.



Scheme 7.4

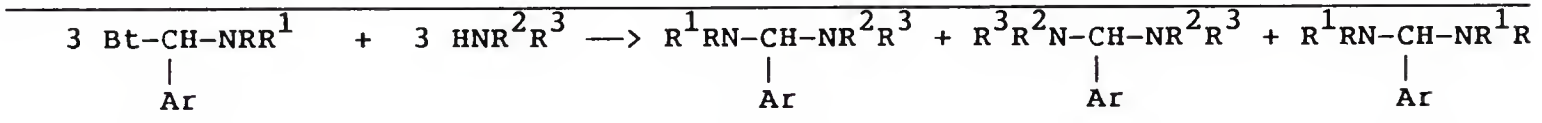
In general, the relative amounts of the produced aminals in the mixture seemed to vary according to their steric congestion: if the incoming amine (Equation 7.6) were very crowded (e.g. $R^2 = R^3 = Pr^i$), then the symmetrical (**7.8**) and most probably the unsymmetrical (**7.9**) aminals

would be undetectable; if the steric factor were of intermediate size (e.g. $R^2 = R^3 = CH_2Ph$), then (**7.9**) would exist in small amounts and (**7.8**) would rather be the major product; if the size of the incoming amine were comparable to that already existing on adduct (**7.7**) (e.g. $R^1 = R^2$ = piperidyl and $R^2 = R^3$ = morpholinyl), then the symmetrical aminals would be the major components.

The chemical shift of the methinic N-CH(Ar)-N carbon atom of the unsymmetrical aminal (**7.8**) should be located between the corresponding signals of the two symmetrical aminals (**7.1**) and (**7.9**) (see Equation 7.6). The detection of the unsymmetrical aminals was therefore based solely on this criterion. The weak point in this method is that sterically hindered symmetrical aminals, cannot be prepared, and their diagnostic chemical shifts can only be hypothesized. In addition, slight changes in chemical shifts due to solvent, concentration, and solute variations could be confused as indicating new products: there is danger of arriving to the wrong conclusions by only considering ^{13}C-NMR chemical shifts; however no other reliable method is available for analysis of the product composition.

The results reported so far suggest that unsymmetrical aminals (**7.1**) of intermediate size can be prepared, but they exist in equilibrium with the symmetrical ones and, in some cases, with the starting materials, and separation is not possible. Table 7.3 summarizes the reactions carried out and the observations made regarding product composition. An uncertainty in the interpretation of the results is evident.

Table 7.3. Composition of products from reactions of benzotriazole adducts (7.7) with 2° amines.

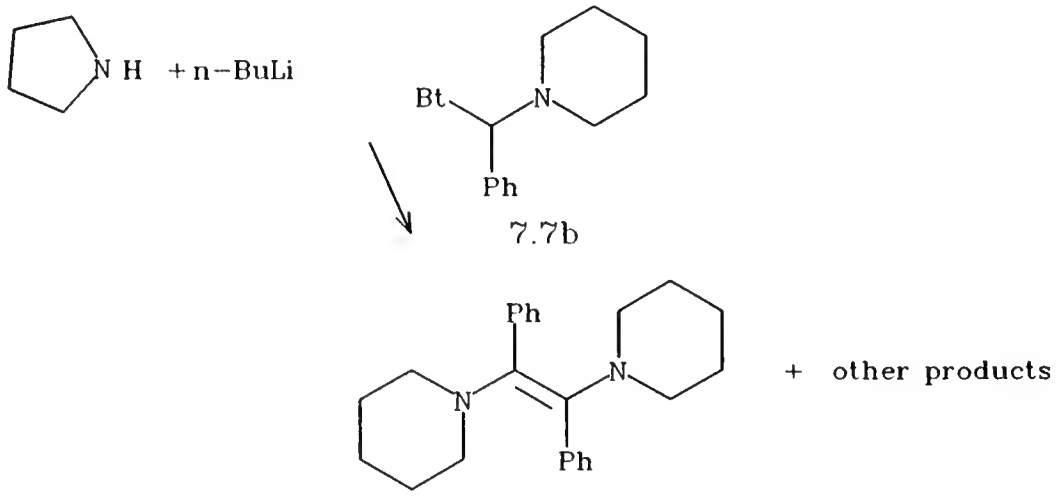


(7.7) (7.8) (7.9) (7.1)

Ar	NRR^1	NR^2R^3	(7.8)	(7.9)	(7.1)
Ph	$N(CH_2)_5$	$N(CH_2)_4$	moderate[a]	major[a]	minor
4-MeO-C_6H_4	$N(CH_2)_4O$	$N(CH_2)_4$	moderate[a]	major[a]	very minor
Ph	$N(CH_2)_5$	$N(Pr^i)_2$	-	-	major
4-MeO-C_6H_4	$N(CH_2)_5$	$N(Pr^i)_2$	-	-	major
Ph	$N(CH_2)_4$	N(cyclohexyl)$_2$		-	major
4-MeO-C_6H_4	$N(CH_2)_4O$	N(cyclohexyl)$_2$	-	-	major
Ph	$N(CH_2)_5$	$N[C(Me)_2CH_2]_2CH_2$	-	-	major
Ph	$N(CH_2)_5$	$N(CH_2Ph)_2$	major	minor	minor

[a] Assignments can be interchanged.

The reaction conditions tested were either aqueous or powdered NaOH in diethyl ether. A few attempts to use NaH in toluene resulted in either no reaction (RT, 15 min) or a complex mixture of products (Δ, 4 h). Earlier attempts to use the lithium or magnesium salts of amines in THF as nucleophiles in reactions with adducts (**7.7**), were only partially successful. Proton abstraction was preferred over substitution in cases where the substrate contained an active hydrogen (see Scheme 7.5).

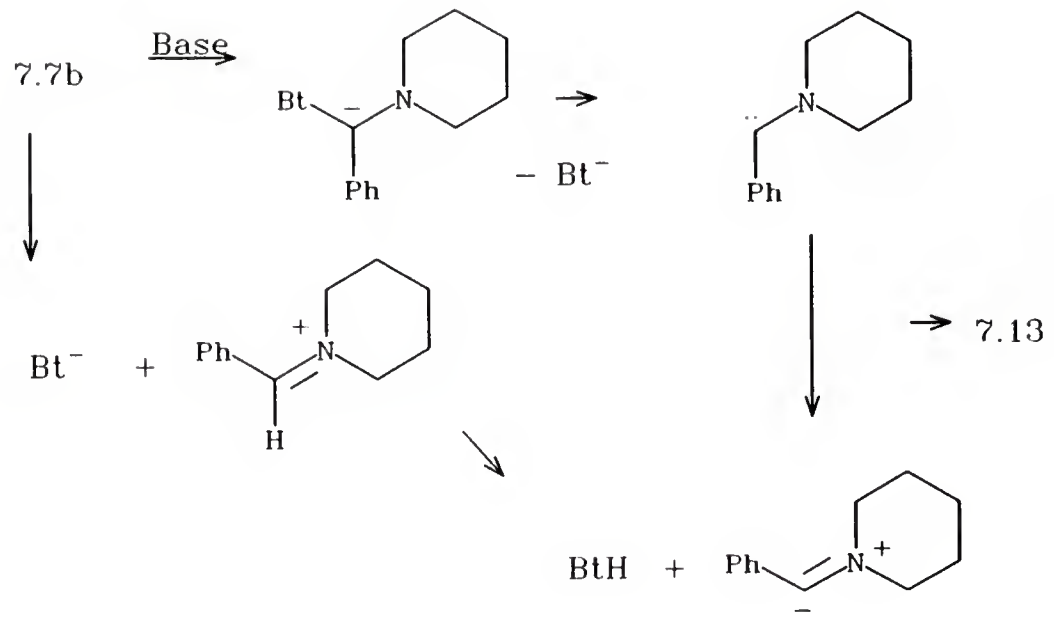


7.7b

7.13

Scheme 7.5

The formation of the dimerization product (**7.13**), (E- or Z-), whose structure is consistent with NMR and mass spectra, can be rationalized either by an α-elimination leading to a carbene, or more likely, initial dissociation of the benzotriazole adduct followed by ylide formation which in turn dimerized to give (**7.13**) (Scheme 7.6).

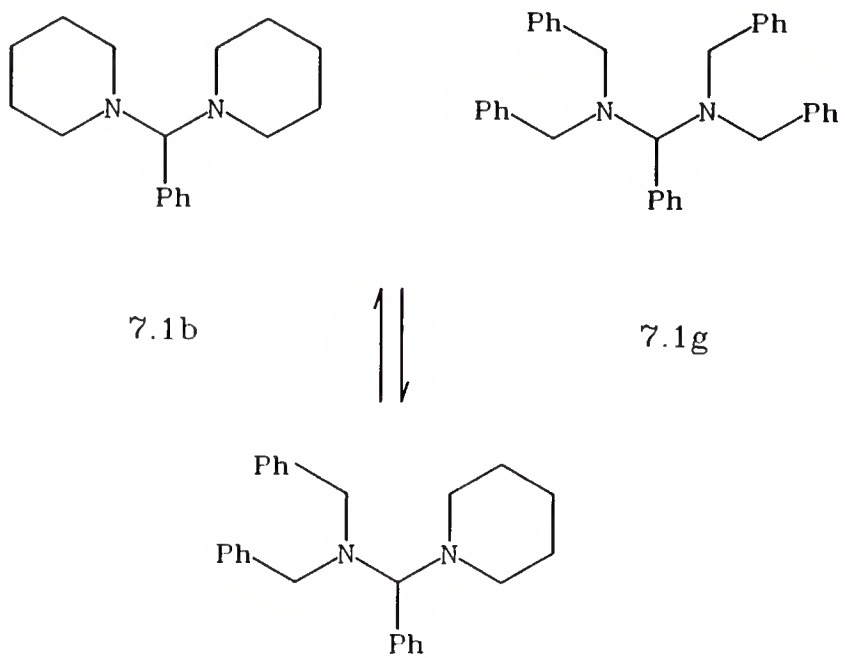


Scheme 7.6

In conclusion, the best conditions for aminal formation were treatment of a Bt-adduct with a different secondary amine and/or solid sodium hydroxide, in diethyl ether at room temperature. In order to drive this reversible process to completion, continuous removal of the precipitating benzotriazole salts from the reaction mixture was necessary (filtration or aqueous workup). Some Bt-adducts were not sufficiently reactive, therefore no reaction took place, regardless of the type of the incoming amine. With reactive adducts, the reaction proceeded to give mixtures of unsymmetrical and symmetrical aminals in ratios determined by the degree of steric congestion in the products.

7.2.3 Cross-Over Reactions of Symmetrical Aminals

The production of mixtures of symmetrical and unsymmetrical aminals in the above reactions (see Equation 7.6) indicated that an additional equilibrium process was in operation, namely between the aminals themselves. The disproportionation of aminals was studied by following the ^{1}H- and ^{13}C-NMR spectra of equimolar mixtures of two different aminals. Specifically, when two symmetrical aminals, such as (**7.1b**) and (**7.1g**) were mixed, an equilibrium was established between reactants and the unsymmetrical aminal product (**7.1bg**) (Scheme 7.7).



Scheme 7.7

The equilibrium position was reached very fast in $CDCl_3$, even when the solvent was previously shaken with sodium carbonate. The intensity and number of peaks in a ^{13}C-NMR spectrum recorded 5 minutes after mixing, had not changed when examined several hours later. On the other hand, the process was slower in either deuterated dioxane or toluene and the rate of appearance of the methine proton signal of the unsymmetrical product could be readily followed by ^{1}H- or ^{13}C-NMR spectroscopy.

Figure 7.1 illustrates the slow equilibration between (**7.1b**), (**7.1g**) and (**7.1bg**) as reflected in their ^{1}H-NMR spectrum. The region of benzylic and methinic protons (2.5-5.5 ppm) was monitored as a function of time. To a toluene-d_8 solution of (**7.1g**) [spectrum at 0 min], an equimolar amount of (**7.1b**) was added and spectra, acquired after two pulses, were recorded at times shown in Figure 7.1. The singlet growing at 3.95 ppm and the two doublets at 4.13 and 3.12 ppm are due to the NC<u>H</u>(Ph)N hydrogen and the two benzylic proton groups, respectively, of the unsymmetrical aminal (**7.1bg**). The singlet at 4.57 is due to NC<u>H</u>(Ph)N of (**7.1g**), whereas the corresponding peak of (**7.1b**) normally appearing at 3.55 ppm, is covered under the foreign peak at 3.55 ppm, which was also present in the spectrum of analytically pure (**7.1g**).

A more clear picture can be obtained by monitoring the region 90-70 ppm of the ^{13}C-NMR spectrum, where the resonances of N<u>C</u>H(Ar)N usually appear (see Table 7.2).

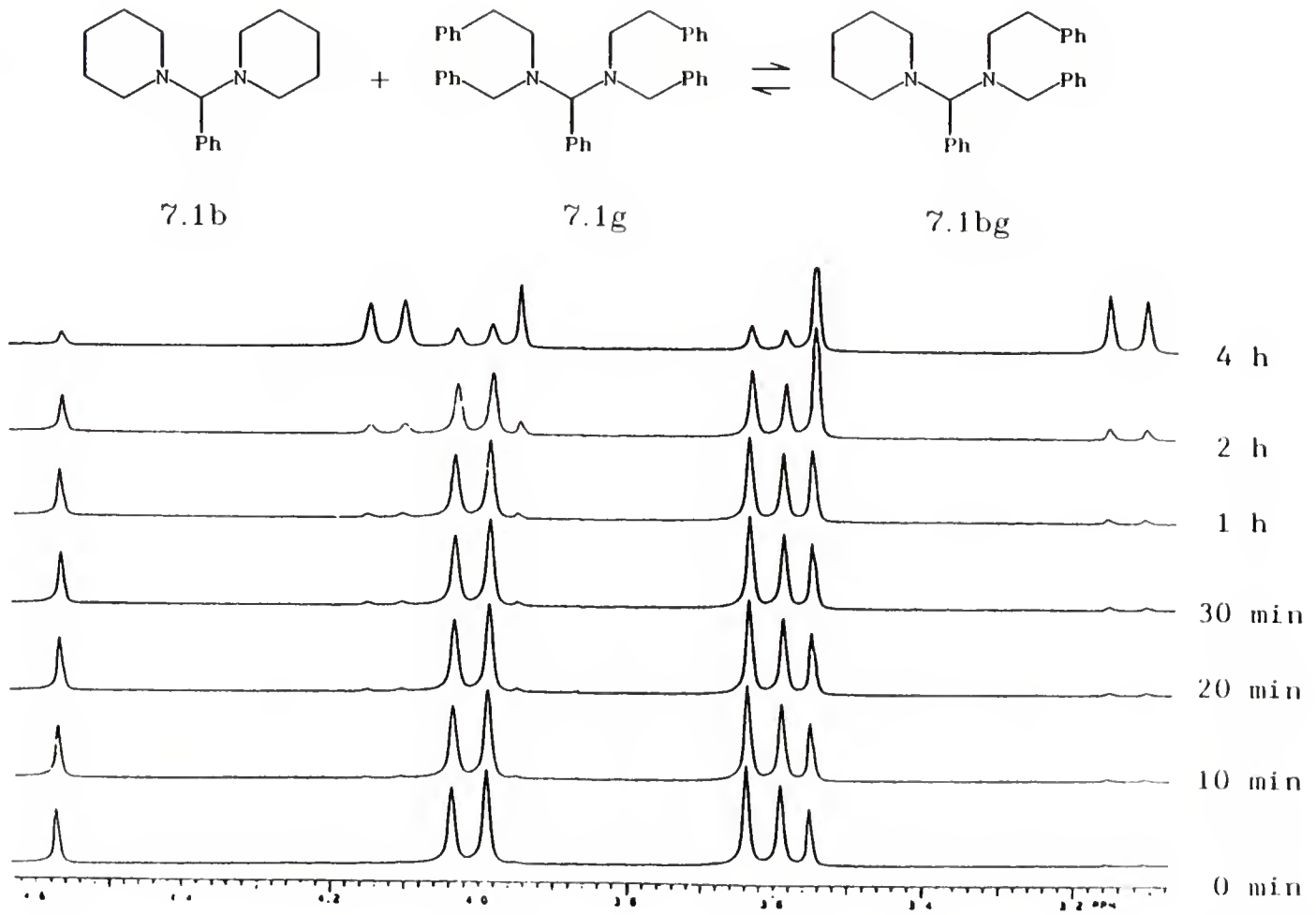


Figure 7.1 Partial ^{1}H-NMR spectra (3-5 ppm) of the mixture (**7.1b**) + (**7.1g**) in toluene-d_8 as a function of time.

Figure 7.2 illustrates the changes in the ^{13}C-NMR spectra of an equimolar mixture of (**7.1b**) and (**7.1g**) as a function of time. The NCH(Ph)N carbon-13 resonance of (**7.1g**) in 1,4-dioxane-d_8 emerges at ~80 ppm (Figure 7.2, spectrum at 0 min). To the solution of (**7.1g**), one equivalent of (**7.1b**) was added and the spectra were recorded at intervals indicated in Figure 7.2. The peak at ~87.5 ppm is due to (**7.1b**). The new signal, emerging between the NCH(Ph)N peaks of the symmetrical starting aminals, presumably originates from the unsymmetrical compound (**7.1bg**). Similar observations were made for the ^{13}C-NMR spectrum of the mixture of (**7.1a**) and (**7.1b**) (see Table 7.2), but in this case the new C-atom [NCH(Ar)N] signal of the mixed aminal (**7.1ab**) was extremely close to that of (**7.1a**), so that detection of the equilibrium process was possible only at 75 MHz (^{13}C-NMR spectrum). When (**7.1b**) and the methoxy substituted aminal (**7.1c**) were mixed together (Figure 7.3), four additional peaks appeared in the ^{13}C-NMR spectrum (88-90 ppm), due to all possible cross-aminal products. The composition of this mixture was also time dependent.

In order to explain the foregoing observations a mechanistic scheme is suggested (Scheme 7.8), which is consistent with the benzotriazole chemistry discussed in previous chapters, and with a recent report [87JOU1198] according to which aminals react *via* previous dissociation to iminium ions, in metal catalyzed alkylations.

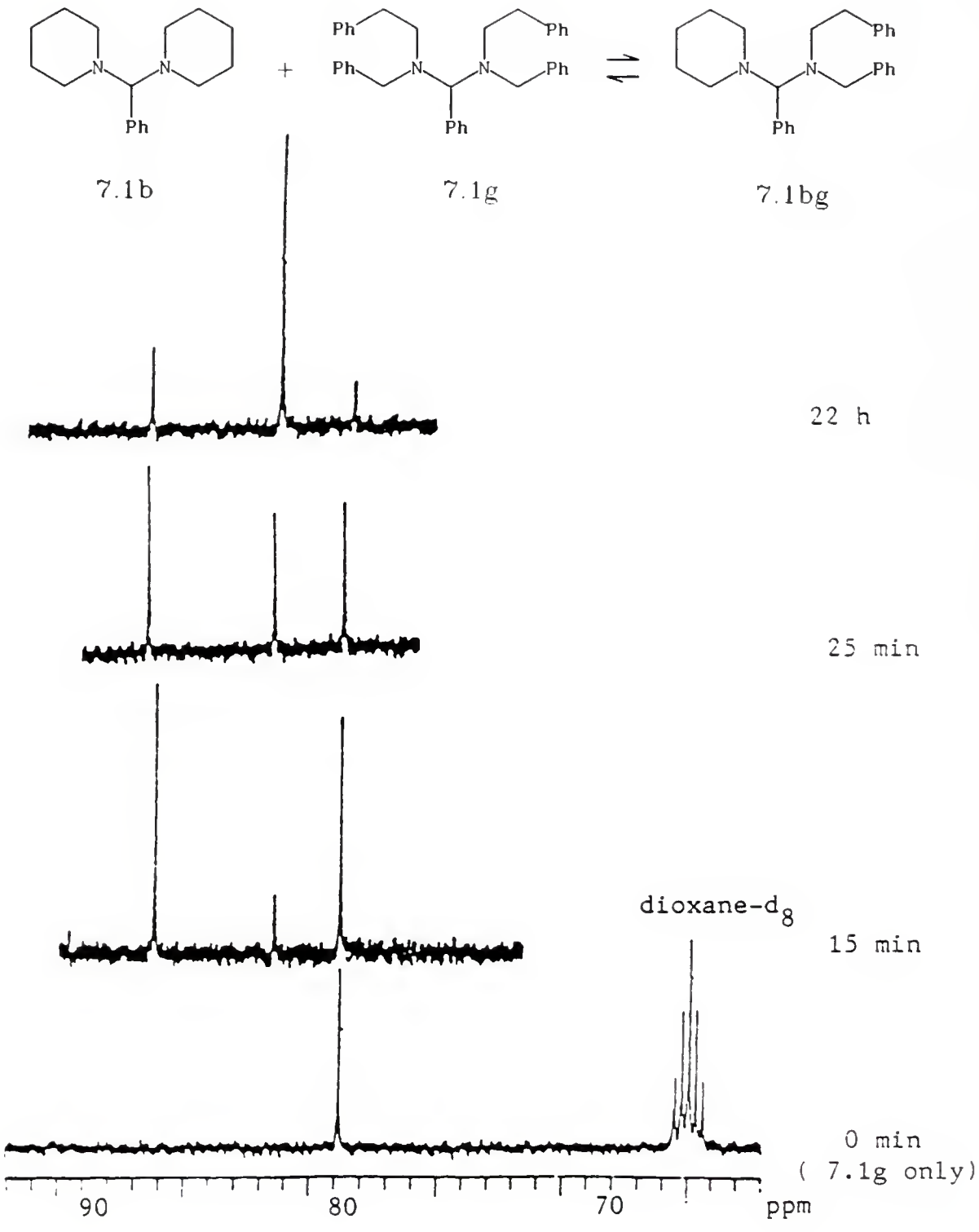


Figure 7.2 Partial ^{13}C-NMR spectra (64-95 ppm) of a mixture of (**7.1b**) + (**7.1g**) as a function of time (in 1,4-dioxane-d_8).

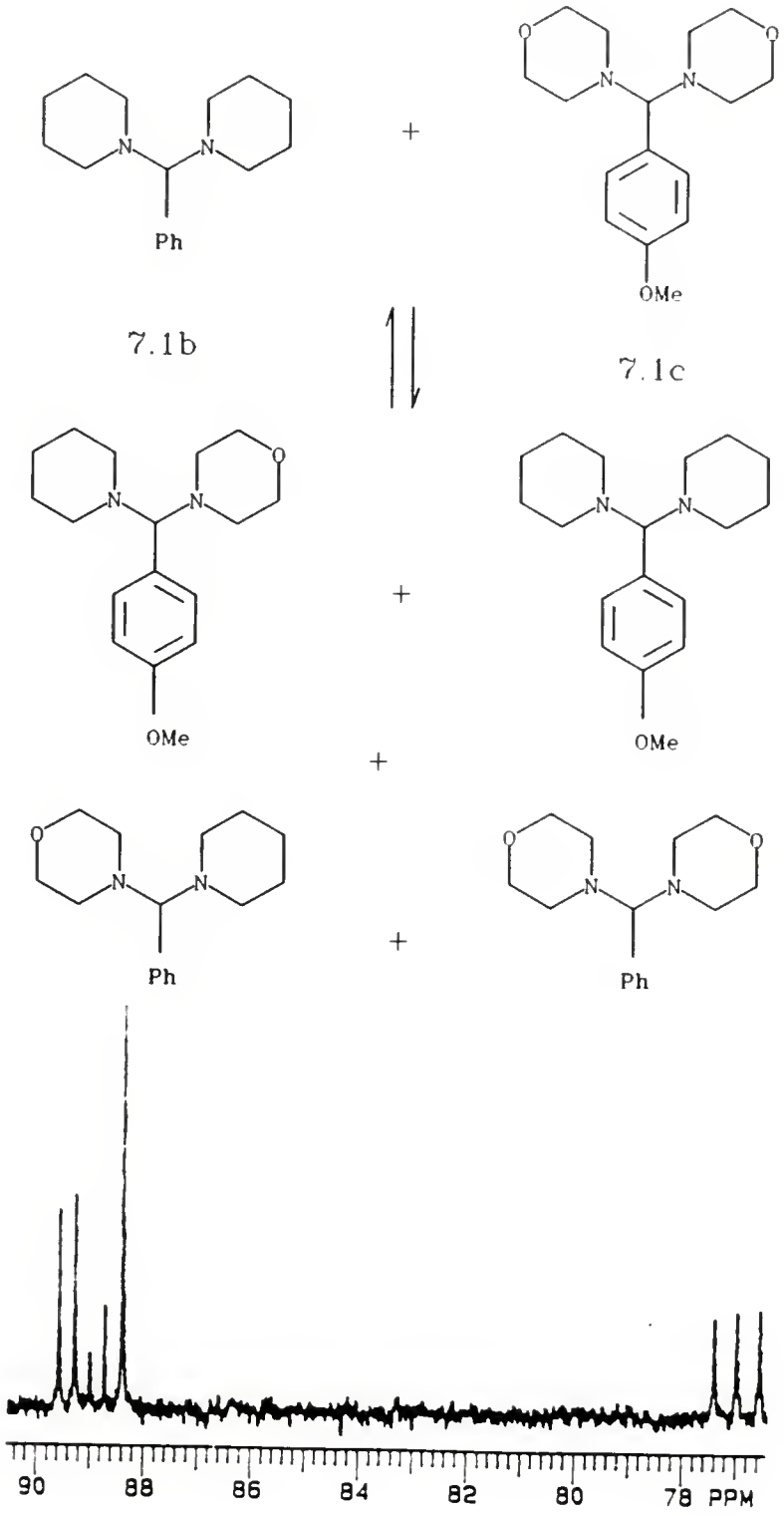
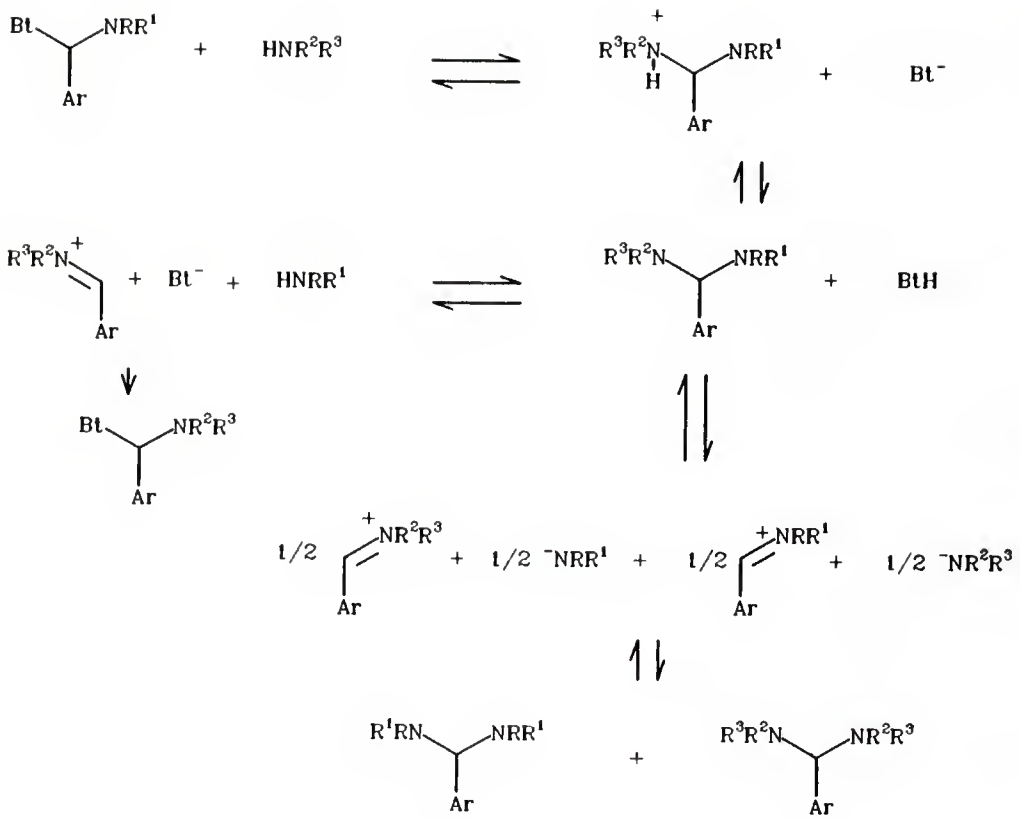


Figure 7.3 Partial ^{13}C-NMR spectrum of the equilibrium mixture of (7.1b) and (7.1c) in $CDCl_3$.



Scheme 7.8

In conclusion, α-aryl substituted symmetrical aminals disproportionate in solution, as shown by ^{1}H- and ^{13}C-NMR cross-over experiments in various solvents.

7.3 Conclusions

The reactions of benzotriazole-arylaldehydes adducts with secondary amines to afford symmetrical aminals were described in this Chapter. Unsymmetrical aminals could also be prepared, but they were always obtained as mixtures with the symmetrical compounds. This was the result of

disproportionation of the products, a process which occurs when two different α-arylaminals are mixed in solution.

7.4 Experimental

Methods and reagents were described in previous Chapters.

7.4.1 Preparation of Benzotriazole Adducts

The preparations of N-[α-(benzotriazol-N-yl)benzyl]-piperidine (**7.7b**) and N-[α-(benzotriazol-N-yl)-α-(4-methoxyphenyl)methyl]morpholine (**7.7c**), were described in Chapter 3 [compounds (**3.15**) and (**3.12**), respectively] and of N-[α-(benzotriazol-N-yl)benzyl]-N,N-dibenzylamine (**7.7g**) was described in Chapter 6 [compound (**6.1d**)]. Adducts (**7.7a**), and (**7.7c**)-(**7.7h**) were prepared according to the general method described in Chapter 3. All showed broad signals in the NMR spectra at room temperature and had to be characterized by low temperature spectra. Purification of these compounds was generally not attempted, and they were used directly for reactions with the secondary amines.

N-[α-(Benzotriazol-N-yl)benzyl]pyrrolidine (**7.7a**). The compound was a viscous dark oil (prepared according to the general method, but at room temperature) which partially decomposed to benzotriazole on attempted distillation;

δ_H (100 MHz, $CDCl_3$, +20°C) 8.20-7.30 (m, 11 H, all aromatic protons), 6.68 (s, NCHN, 1 H), 2.68 (br s, 4 H), 1.74 (br m, 4 H). Presumably this is the spectrum above coalescence; δ_C (25 MHz, CD_2Cl_2, -50°C) 145.8, 136.9, 132.2, 128.5, 127.3, 123.9, 119.3, 112.0, 81.4, 67.4, 50.3, 25.2, 23.1 (mixture of two isomers).

N-[α-(Benzotriazol-N-yl)-α-(4-methoxyphenyl)]methyl]-piperidine (7.7d). It was obtained as an oil which was characterized spectroscopically: δ_H (300 MHz, $CDCl_3$, -20°C) 8.2-7.8 (2m, 3 H, Bt), 7.6-7.2 (m, 3 H, Ph, Bt), 7.1-6.7 (m, 3 H, Ph and NCHN), 3.77 (s, 3 H, OMe), 2.8-2.1 (br m, 6 H, piperidine), 1.9-1.2 (3m, 4 H, piperidine); δ_C (75 MHz, $CDCl_3$, -20°C) 159.0, 145.5, 142.0, 132.8, 128.4, 127.9, 126.9, 126.6, 123.4, 119.3, 113.4, 111.9, 89.0 (NCHN, 2-isomer), 82.9 (NCHN, 1-isomer), 54.8 (OMe), 45.0 (br s), 25.6, 23.7. The aromatic peaks were not present at room temperature.

N-[α-(Benzotriazol-N-yl)benzyl]-N-methylaniline (7.7f). The compound was obtained as a clean, white solid (86%), m.p. 85-88°C (from benzene/pet. ether) (Found, C, 76.05; H, 5.68; N, 18.17%. $C_{20}H_{18}N_4$ requires, C, 76.41; H, 5.77; N, 17.82%); δ_H (60 MHz, $CDCl_3$) 8.2-7.8 (2m, 4 H, Bt, Ph), 7.5-6.8 (m, 11 H, Bt, Ph), 3.2 (Me, 2-isomer), 3.0 (Me, 1-isomer); δ_C (25 MHz, $CDCl_3$) (all expected aromatic peaks due to two isomers are present, but unequivocal assignment is not possible) 148.7, 148.3, 144.0, 136.8, 135.9, 132.9,

129.3, 129.2, 128.8, 128.7, 128.6, 128.5, 127.5, 127.1, 126.7, 126.4, 123.9, 119.9, 119.8, 119.4, 118.4, 114.7, 114.0, 110.0, 82.4, 77.1, 34.8, 34.3.

N-[α-(Benzotriazol-N-yl)benzyl]-N,N-diethylamine (7.7h). It was obtained as a viscous oil: δ_H (300 MHz, $CDCl_3$, -20°C) 8.2-8.1 (m, 2 H, Bt), 8.1-7.9 (m, 3 H, Bt, Ph), 7.8-7.2 (m, 4 H, Bt, Ph), 7.1 (s, 1 H, NCHN), 3.2-3.1 (q, J = 7 Hz, 3 H, NCH_2), 3.1-2.9 (m, 3 H, $PhCH_2$, NCH_3), 2.5-2.2 (m, 6 H, CH_3), mixture of two isomers; δ_C (75 MHz, $CDCl_3$, -30°C) 146.0, 136.4, 134.5, 128.5, 128.2, 127.2, 126.9, 126.8, 123.6, 119.6, 115.5, 111.4, 85.4 (NCHN, 2-isomer), 78.7 (NCHN, 1-isomer), 43.2, 42.6, 13.3, 12.1.

7.4.2 Preparation of Aminals

General method (A). The aminals (**7.1a**)-(**7.1d**) and (**7.1g**) were prepared by heating a 2:1 molar ratio of amine/arylaldehyde (see Table 7.1) in benzene, by means of a Dean-Stark trap, until the theoretical amount of water had been collected. The solvent was removed under vacuum and the residue was triturated with diethyl ether or petroleum ether, and the product was usually obtained as a solid. In general, further purification products was avoided, since they tended to hydrolyze or decompose.

General method (B). The benzotriazole adducts were dissolved in diethyl ether and treated with 1 equivalent of a secondary amine and powdered NaOH, or (better) with 2

equivalents of the secondary amine. After stirring for 15 min at room temperature the resulting precipitate (water soluble) was either removed with alkaline washing (2N NaOH) or filtered and the solvent evaporated. Yields of aminals (**7.1a**)-(**7.1d**) were listed in Table 7.1. This method was also used in the attempted preparation of unsymmetrical aminals shown in Table 7.3.

α,α-Bis(pyrrolidinyl)toluene (**7.7a**). It was obtained as a white solid, m.p. 36.5-37.5°C (lit. [75BSF196] m.p. 40-41°C); δ_H (300 MHz, $CDCl_3$) 7.29 (m, 5 H), 3.91 (s, 1 H, NCHN), 2.48 (m, 8 H, NCH_2), 1.65 (m, 8 H, $NCH_2C\underline{H}_2$); δ_C (75 MHz, $CDCl_3$) 136.3, 128.9, 127.2, 127.1, 85.3, 49.3, 22.9.

α,α-Bis(piperidyl)toluene (**7.7b**). The compound was obtained as a white solid, m.p. 77-79°C (lit. [55JA1098] m.p. 80-81°C); δ_H (200 MHz, $CDCl_3$) 7.30-7.16 (m, 5 H, Ph), 3.55 (s, 1 H, NCHN), 2.33 (m, 8 H, $NC\underline{H}_2$), 1.50 (m, 8 H, $NCH_2C\underline{H}_2$), 1.36 [m, 4 H, $N(CH_2CH_2)_2C\underline{H}_2$]; δ_C (25 MHz, $CDCl_3$) 136.1, 128.5, 127.1, 126.9, 89.7, 50.0, 26.1, 25.2.

α,α-Bis(morpholinyl)-4-methoxytoluene (**7.7c**). The product was a white solid, m.p. 106-108°C (lit. [75BSF196] m.p. 119-120°C) (Found, C, 65.24; H, 7.73; N, 11.47%. $C_{16}H_{24}N_2O_3$ requires, C, 65.73; H, 8.27; N, 9.58%); δ_H (300 MHz, $CDCl_3$) 7.11 (d, J_o = 9 Hz, 2 H, MeO-$CC_2H_2C_2\underline{H}_2$), 6.88 (d, J_o = 9 Hz, 2 H, MeO-$C_2\underline{H}_2$), 3.80 (s, 3 H, OMe), 3.66 (t,

J = 5 Hz, 8 H, CH_2O), 3.59 (s, 1 H, NCHN), 2.43 (m, 8 H, NCH_2); δ_C (75 MHz, $CDCl_3$) 159.1, 129.8, 126.3, 113.1, 88.5, 67.2, 55.2 (OMe), 49.5.

α,α-Bis(piperidyl)-4-methoxytoluene (7.7d). The product did not solidify; δ_H (60 MHz, $CDCl_3$) 7.3-6.8 (A_2B_2, J = 9 Hz, 4 H, aromatic), 3.8 (s, 3 H, OMe), 3.7 (s, 1 H, NCHN), 2.3 (m, 8 H, NCH_2), 1.4 [m, 12 H, $N(CH_2C\underline{H}_2)_2C\underline{H}_2$); δ_C (25 MHz, $CDCl_3$) 158.5, 129.4, 128.4, 112.5, 89.1, 50.0, 26.2, 25.3.

α,α-Bis(N,N-dibenzylaminyl)toluene (7.7g). The compound was a white solid, m.p. 138-141°C (Found, C, 87.45; H, 7.17; N, 5.86%. $C_{35}H_{34}N_2$ requires, C, 87.10; H, 7.10; N, 5.80%); δ_H (300 MHz, $CDCl_3$) 7.39-7.12 (m, 25 H, Ph), 4.49 [s, 1 H, NC$\underline{H}$(Ph)N], 4.00 (s, 2 H, C$\underline{H}_2$Ph), 3.95 (s, 2 H, C$\underline{H}_2$Ph), 3.57 (s, 2 H, C$\underline{H}_2$Ph), 3.53 (s, 2 H, C$\underline{H}_2$Ph); δ_C (75 MHz, $CDCl_3$) 139.4, 135.1, 129.6, 129.1, 128.0, 127.7, 126.9, 126.5, 79.7, 52.7.

α,α-Bis(morpholinyl)toluene (7.7j). The compound was prepared using method A, m.p. 97-98°C (lit. [72MI2] m.p. 101-101.5°C); δ_H (300 MHz, $CDCl_3$) 7.33-7.17 (m, 5 H, Ph), 3.66 (t, J = 5 Hz, 8 H, O$\underline{CH}_2$), 3.63 (s, 1 H, NCHN), 2.42 (m, 8 H, N$\underline{CH}_2$); δ_C (75 MHz, $CDCl_3$) 133.8, 128.6, 127.7, 127.6, 88.5 (NCHN), 67.0, 49.4.

α,α'-Bis(piperidyl)stilbene (7.13). A three-necked flask was evacuated and flushed with Ar three times, then charged with freshly distilled pyrrolidine (0.005 mol, 0.42 ml) in a THF solution (20 ml). The liquid was cooled to -78°C (10 min) and n-BuLi (2.5 M in hexanes, 2.1 ml, 0.0055 mol) was added slowly. The suspension was left to stir for 1 h. The oily N-[α-(benzotriazol-N-yl)benzyl]piperidine (**7.7b**) (1.46 g, 0.005 mole) in THF (25 ml) was introduced slowly into the flask at -78°C. A deep purple color was immediately developed. After stirring for 1 h, the mixture was allowed to warm up slowly. At room temperature, a brown coloration was observed. After 1 h, a little water was added and then aq. sat. ammonium chloride (to pH ~ 8.5). The solution was extracted with ether (3 x 20 ml), washed with 2N NaOH (1 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a semi-solid, which, upon attempted recrystallization from 90% EtOH, yielded a bright yellow solid (0.13 g, 15%), m.p. 108-110°C (Found, C, 82.34; H, 10.04; N, 7.74%. $C_{24}H_{30}N_2$ requires, C, 83.19; 8.73; 8.08); m/z (rel. intensity) 346 ($M^{+\cdot}$, 100), 289 (33), 178 (53), 84 (50); δ_H (200 MHz, toluene-d_8) 8.0-6.8 (m, 10 H), 3.5 (m, 8 H), 2.5 (m, br, 12 H); δ_C (50 MHz, toluene-d_8) 137.6, 131.9, 130.3, 128.3, 127.1, 53.5, 27.7, 25.0. From the above data, the structure of the compound was assigned as that of (**7.13**), but the geometry (E- or Z-) could not be determined.

CHAPTER 8

SUMMARY AND CONCLUSIONS

In this work, we have studied the kinetic and thermodynamic aspects of the isomerization of N-(α-aminoaklyl)benzotriazoles. We have also investigated the reactions of these compounds with different nucleophiles, and developed several synthetic methodologies for synthesis of N-α- functionalized secondary amines.

In Chapter 2, the exchange of the N,N-dialkylaminoalkyl substituents between the 1- and 2- positions of benzotriazole was studied using simple N-(α-aminomethyl)-benzotriazoles as model compounds. We found that the 1- to 2- isomerization takes place in the liquid and gas phases but not in the solid phase, in which they exist solely as the 1-substituted isomers. The 1- to 2- isomerization was shown to be intermolecular. The proposed mechanism, consistent with the spectroscopic evidence, involves the dissociation of the compounds to iminium ions and the benzotriazole anion.

In Chapter 3, the influence of the structure on the isomerization process was studied. The 1-isomer was found to be favored in compounds bearing small N-substituents and in polar solvents. The 1- and 2- isomers were nearly equally favored in compounds with large N-substituents and

non-polar solvents, however the 1-isomer predominated in most mixtures. The energy barrier to isomerization was estimated to be in the range of 15.7 to 18.6 kcal/mole. Substituents that provide stabilization to the intermediate ions, by donating or withdrawing electrons, and polar solvents, tend to lower the magnitude of the activation energy. The reactivity of the benzotriazole adducts could then be predicted in the basis of their structure.

In the Chapters that followed, the ability of the benzotriazole adducts to behave in solution as sources of iminium ions was exploited in many ways. Thus, Chapter 4 described their reactions with Grignard reagents and with sodium borohydride which led to variously substituted tertiary amines in high yields. The sequence could be carried out in one step, bypassing the isolation of the benzotriazole adducts. In Chapter 5, a new general method was established in which lithium acetylenides reacted with the benzotriazole adducts to produce 3-substituted propargylamines in very high yields. Again the one-step possibility was utilized. In Chapter 6, preparation of β-aminoesters was demonstrated, in reactions of the adducts with Reformatsky reagents. In Chapter 7, reactions with secondary amines led to symmetrical and unsymmetrical aminals. Interestingly, these products were found to undergo disproportionation in solution. This behavior justified the inability to prepare unsymmetrical aminals not contaminated with the corresponding symmetrical compounds.

In conclusion, the present work has demonstrated the enhanced electrophilicity of N-(α-aminoalkyl)benzotriazoles and established their reactivity limits toward a wide range of nucleophiles. It has also paved the way for new synthetic possibilities, and further exploitation and understanding of the chemistry of benzotriazole.

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Letter Codes for Journal Titles

Code	Full title
AC	Acta Crystallogr.
ACS(A)	Acta Chem. Scand. Ser. A.
AHC	Adv. Heterocycl. Chem.

AG(I)	Angew. Chem Int. Ed. Engl.
AP	Arch. Pharm.
BCJ	Bull. Chem. Soc. Jpn.
BEP	Belg. Pat.
BP	Brit. Pat.
BSF	Bull. Soc. Chim. Fr.
CB	Chem. Ber.
CC	J. Chem. Soc. Chem. Commun.
CHC	Comprehensive Heterocyclic Chemistry
CR	Chem. Rev.
EU	Eur. Pat.
GP	Ger. Pat.
H	Heterocycles
HCA	Helv. Chim. Acta
ICA	Inorg. Chim. Acta
JA	J. Am. Chem. Soc.
JAP	Jpn. Pat.
JCS	J. Chem. Soc.
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JMC	J. Med. Chem.
JMR	J. Magn. Res.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
LA	Liebigs Ann. Chem.
MI	Miscellaneous

MRC	Magn. Res. Chem.
OCR(A)	Organometal. Chem. Rev. A
OMR	Org. Magn. Reson.
OMS	Org. Mass Spectrom.
OR	Org. React.
S	Synthesis
SA	Spectrochim. Acta
SC	Synth. Commun.
T	Tetrahedron
TL	Tetrahedron Lett.
UP	Unpublished results

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BIOGRAPHICAL SKETCH

The author was born in November 1957 in Filiatra Messinias, Greece. She graduated from the University of Athens in June of 1981 with a B.S. in chemistry. The same year she enrolled as a graduate student in the Chemistry Department of the Nuclear Research Center "Democritus", where she had a brief contact with organic photochemistry in the lab of Dr. Hadjudis. She joined the graduate school of Clemson University in August 1982, where she obtained a M.S. degree in organic chemistry under the supervision of Dr. Abramovitch. She moved to the University of Florida to pursue her Ph.D. in January 1985. She joined Dr. Katritzky's group six months later.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chairman
Kenan Professor of Organic Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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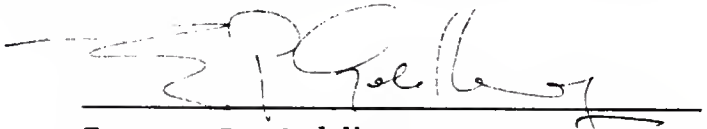
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 1988

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